Applicants' claims are drawn specifically to a method of treating or inhibiting vasomotor symptoms comprising continuously and uninterruptedly providing a daily dosage of about 1.5 mg MPA in combination with a dosage of between about 0.3 and about 0.45 mg CEE, USP. The Examiner acknowledged that "Plunkett et al. does not particularly teach the dosages of conjugated equine estrogen/medroxyprogesterone claimed herein." (Office Action, p. 3). Applicants maintain that there is nothing in Plunkett to teach or suggest the selection of 1.5 mg MPA for the treatment of vasomotor symptoms in combination with about 0.3 to about 0.45 mg CEE.

The Examiner stated that Applicants have not provided any data demonstrating unexpected results in comparison with Plunkett. As discussed below, Applicants respectfully submit that the initial burden of a prima facie case of obviousness has not been established. Moreover, Applicants respectfully disagree that Applicants have not provided data demonstrating unexpected results. Applicants have provided data in the specification and submitted a Declaration under 37 C.F.R. 1.132 of Rogerio A. Lobo, M.D. on April 1, 2003 to further support their showing of unexpected results of Applicants' claimed invention over Plunkett. Applicants submit herewith a Second Declaration under 37 C.F.R. 1.132 of Rogerio A. Lobo, M.D which provides further evidence concerning Applicants' invention.

Plunkett describes 0.600 mg as the preferred dosage of CEE (Table 1A) and 2.5 mg as the preferred dosage of MPA (Table 1B). This preferred combination of CEE and MPA represents the closest teaching within Plunkett to the Applicants' claimed invention. The Examiner noted that the example on page 9 of the specification compares the claimed invention to a combination using a dosage of *0.625 mg CEE*, and not *0.600 mg*, as disclosed in Plunkett. (Office Action, p. 4). However, the difference between these two CEE dosages, 0.025 mg or 2.5

hundredths of a milligram, does not provide a meaningful difference when compared to Applicants' invention. (Second Lobo Declaration ¶ 3). For purposes of treating or inhibiting vasomotor symptoms, one skilled in the art would consider a daily dosage of 0.600 mg CEE to be clinically equivalent to a dosage of 0.625 mg CEE. (Second Lobo Declaration ¶ 3). Thus, Applicants properly have provided data in the application from a clinical study showing unexpected results of the claimed invention of lower dosages of CEE and MPA in comparison with the preferred dosages of CEE and MPA disclosed in Plunkett. (Second Lobo Declaration ¶ 3). The combination of preferred dosages in Plunkett essentially has become the standard, commercially available dosage -- 0.625 mg CEE in combination with 2.5 mg MPA ("PREMPRO").

The Examiner has stated that the data on page 9 does not constitute unexpected results, because the data shows similar efficacy in treating vasomotor symptoms between the standard commercially available regimen, 0.625 mg CEE/2.5 mg MPA, and the lower dosage regimens claimed herein, 0.45 mg CEE/1.5 mg MPA and 0.30 mg CEE/1.5 mg MPA. (Office Action, p. 4). The examiner further noted some data points are overlapping in both numbers and severity of hot flushes for these regimens. However, these similar therapeutic results are precisely what was unexpected to one skilled in the art. The results of the study reported on page 9 unexpectedly demonstrated that providing a much lower daily dosage of 1.5 mg MPA in combination with 0.45 or 0.30 mg CEE reduced the number and severity of hot flushes to essentially the same extent as the standard, commercially available dose combination of 0.625 mg CEE and 2.5 mg MPA. (Second Lobo Declaration ¶ 6). It was expected by one skilled in the art that the lower combination doses of CEE and MPA may exhibit *some effect* in reducing the number and severity of hot flushes, but *far less of an effect* than the standard dose of 0.625 mg

CEE plus 2.5 mg MPA. (Lobo Declaration ¶ 12). Applicants respectfully submit that the Examiner improperly has inferred that to demonstrate unexpected results, the lower dosages must show better results than the preferred dosages in Plunkett. The first Declaration under 37 C.F.R. § 1.132 of Rogerio A. Lobo, M.D. demonstrates that it was a surprising and unexpected result from the Women's Health, Osteoporosis, Progestin, Estrogen study ("H.O.P.E. study") study that a daily dose of 1.5 mg MPA in combination with the lower doses, 0.45 mg or 0.30 mg, of CEE, rapidly reduced the number and severity of hot flushes to the same extent as the higher dose combinations of 0.625 mg CEE and 2.5 mg MPA. (Lobo Declaration ¶ 14).[1] Applicants submit that disregarding such evidence is not appropriate.

The Examiner has stated that because the lower dosage combinations yielded similar therapeutic results with the standard commercially available combination, the Applicants confirmed the teachings of Plunkett that the entire range is effective in treating hot flushes. (Office Action, p. 4). Respectfully, Applicants submit that the Examiner has applied the incorrect standard. Applicants are required to compare their claimed invention with the closest species/teaching disclosed in the prior art. Applicants have made such a comparison and have demonstrated the unexpected results of their invention over Plunkett. Furthermore, Applicants did not confirm the entire ranges of Plunkett are effective in treating hot flushes. Rather, Applicants showed results for the particular low dosage combinations of CEE and MPA claimed herein.

---

[1]It should be noted that the claimed dosage of 1.5 mg of MPA is sixty-six percent below the preferred dosage of 2.5 mg MPA provided in Plunkett. (Table 1B). The dosages of CEE are between thirty-three and one hundred percent lower than the preferred dosage of 0.6 provided in Plunkett. (Table 1A).

The Examiner further stated that the data on page 9 showed that at week 12 the three regimens seemed to yield comparable results, whereas at 8 weeks the higher doses of CEE yielded much better results. (Office Action, p. 4). The Examiner concluded that the skilled artisan purportedly cannot ascertain the efficacy of one regimen over the other. (Office Action, p. 4). However, the results inform the skilled artisan that the lower dosage combinations of the invention were as effective in decreasing the number and severity of hot flushes as the standard commercially available higher dosage combination, to essentially the same degree. (Second Lobo Declaration ¶ 5). This result is contrary to what would have been expected. (Second Lobo Declaration ¶ 6).

The Examiner appears to dismiss Dr. Lobo's expert opinion that 0.625 mg has been accepted in the art as the minimum dosage of estrogen necessary to relieve the vasomotor symptoms. (Lobo Declaration ¶10). Similarly, the Examiner appears to dismiss Dr. Lobo's evidence that the combination of 0.625 mg of CEE plus 2.5 mg of MPA has been the most commonly prescribed combination hormone replacement therapy (Lobo Declaration ¶10), based on the reference to Archer et al. which was published a couple months after the subject application. However, Dr. Lobo made these statements based not only on these cited references, but also based on his knowledge as a practicing physician in the field. Dr. Lobo has extensive experience in treating women for symptoms of menopause, including hot flushes, and has knowledge of what others skilled in the art prescribed for their patients. Additionally, Dr. Lobo also submits herewith additional references published prior to the date of application that support these statements. (Second Lobo Declaration ¶ 2).

The Examiner correctly noted that the reference, The Writing Group for the PEPI Trial, "Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial," JAMA 275(5):370-5 (1996), teaches the co-administration of MPA with CEE to provide protection of the endometrium. (Lobo Declaration ¶ 7). However, the reference does not teach the two specific, low dose combinations of CEE plus MPA claimed herein. In the PEPI trial, the women were randomly assigned to one of five treatment groups: (1) a placebo; (2) 0.625 mg CEE daily; (3) 0.625 mg CEE daily plus 10 mg of MPA for 12 days per month; (4) 0.625 mg CEE daily plus 2.5 mg MPA daily; or (5) 0.625 mg CEE daily plus 200 mg of a natural (micronized) progesterone for 12 days per month. (Lobo Declaration ¶ 7). The reference teaches that the addition of 2.5 mg MPA to the 0.625 mg CEE provided protection of the endometrium.

The Examiner concluded that there is no showing of an additive effect of MPA in the specification and in Dr. Lobo's declaration. (Lobo Declaration ¶ 15). The Examiner noted that because the dosages of CEE and MPA in the tables on page 9 are lowered simultaneously from the second column to the third and forth column, the additive effects of the drugs, if any, cannot be ascertained. (Office Action, pp. 4-5). Applicants respectfully submit that this is incorrect. The tables on page 9 report the mean number and severity of hot flushes. The second, third and fourth columns represent the results for the treatment group receiving 0.625 mg CEE/2.5 mg of MPA, 0.45 mg CEE/1.5 mg MPA and 0.3 mg CEE/1.5 mg CEE respectively. The MPA dosage is the same in the third and fourth columns, while the CEE dosage is lowered. The results in columns

three and four are comparable and show that when the CEE dosage is lowered and the MPA dosage is kept at 1.5 mg, the number and severity of hot flushes are reduced to essentially the same extent. This offers some evidence of the additive effect of MPA at low dosages of CEE.

The Examiner is correct that Applicants do not specifically recite the additive effect of MPA in the claims. The H.O.P.E. study was not specifically designed to demonstrate such an effect. However, Greendale et al. taught that previous studies showed that MPA had no additive effect on vasomotor relief when much higher dosages of MPA and much higher dosages of CEE were used. (See Greendale et al., Obstet. Gynecol., 92:982-988 (1988)). Specifically, Greendale reported studies using the following regimens: (1) placebo; (2) 0.625 mg CEE daily; (3) 0.625 mg CEE daily plus 2.5 mg MPA daily; (4) 0.625 mg CEE daily plus 10 mg MPA for 12 days per month; and (5) 0.625 mg CEE daily plus 200 mg micronized progesterone for 12 days per month. Greendale et al. reported that there was "convincing evidence" that regimens using CEE plus MPA were not more effective than CEE alone against vasomotor symptoms. One skilled in the art believed that MPA had merely a prophylactic effect (to prevent endometrial cancer). However, the H.O.P.E. study unexpectedly demonstrated that at the particular low dose of 1.5 mg MPA, may contribute vasomotor relief in combination with the lower dosages of 0.3 or 0.45 mg CEE. These results are preliminary evidence that there is a therapeutic role for MPA beyond endometrial protection when lower dosages of CEE are used. These results have not been statistically proven, but illustrate an unexpected trend, which may be explained by the additive effect of MPA at low dosages.

Applicants also maintain that the Examiner has not even met the initial burden of presenting a prima facie case of obviousness. In re Rijckaert, 9 F.3d 1531, 1532, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). To establish prima facie obviousness, the prior art reference(s) must teach or suggest all of the claim limitations. In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Because Plunkett does not teach, or suggest, using 1.5 mg MPA in combination with about 0.3 to about 0.45 mg CEE for relief of vasomotor symptoms of menopause, it is respectfully submitted that Plunkett does not render claim 7 obvious. Plunkett discloses thousands of possible estrogen/progestin combinations. The preferred dosages of MPA and CEE that Plunkett discloses are much higher than the dosages claimed in the present invention. It would not have been obvious at the time of the invention to select the lower dosage combinations claimed herein. Applicants respectfully submit that the Office Action employs a reconstruction based upon improper hindsight reasoning. In re Fine, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Plunkett's statement that "the maximum, minimum and preferred dosage levels for the respective estrogens and progestogens in the foregoing combinations are recited in the tables" invites one of skill to try a multitude of combinations within the aforementioned ranges. (Col. 7, lines 7-14). At best, it would have been obvious to try the Applicants' claimed combination, but it has long been held that "obvious to try" is not the appropriate standard. Therefore, the Office Action does not reflect the proper evidence to support an obviousness rejection based on the reference relied upon. In any event, as discussed above, in order to facilitate prosecution, the Declaration and Second

Declaration of Dr. Lobo, submitted under 37 C.F.R. § 1.132, are believed to demonstrate convincingly the unexpected results obtained with Applicants' invention.

Claims 11, 12 and 69 depend from claim 7, and it is respectfully submitted that Plunkett does not render obvious these dependent claims for at least the same reasons given above in support of the patentability of claim 7.

It is respectfully submitted that all pending claims are allowable. All issues raised by the Examiner having been addressed, reconsideration and allowance of the claims are respectfully requested. If for any reason the Examiner believes that contact with Applicants' attorney would advance prosecution, she is invited to contact the undersigned at the telephone number given below.

Respectfully submitted,

Dated: Jan 9, 2004

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(formerly AM100226)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S)	:	PICKAR, J., DEY M.
SERIAL NO.	:	09/808,878
FILED	:	March 15, 2001
TITLE	:	HORMONE REPLACEMENT THERAPY
ART UNIT	:	1617
EXAMINER	:	M. Bahar

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SECOND DECLARATION UNDER 37 C.F.R. § 1.132

SIR:

I, ROGERIO A. LOBO, M.D., declare as follows:

1. The statements made in my Declaration Under 37 C.F.R § 1.132 submitted on April 1, 2003 are incorporated herein, including information regarding my background and qualifications and my curriculum vitae attached as Exhibit A thereto.

2. For the past 20 years, the dosage of 0.625 mg CEE has been accepted as the minimum dosage of estrogen necessary to relieve the symptoms of menopause, including hot flushes and bone loss. (See, e.g., Sobel NB, Obstetrics and Gynecology Clinics of North America, 21:299-319 (1994) (describing 0.625 mg as the standard dose of conjugated estrogen) (Ex. A hereto); Kronenberg F, Chapter 9: Hot Flashes, in Rogerio A. Lobo, ed., Treatment of the Postmenopausal Woman: Basic and Clinical Aspects, New York, NY: Raven Pres, at 109 (1994)) ("The most commonly used regimen for treating hot flashes in the United States is 0.625 to 1.25 mg of oral conjugated equine estrogen (Premarin)") (Ex. B hereto). The dosage of 2.5 mg of MPA has

been recognized as the minimum amount needed to oppose 0.625 mg CEE and protect the endometrium. This combination of 0.625 mg CEE plus 2.5 mg MPA daily has been the most commonly prescribed combination estrogen-progestin hormone replacement therapy regimen in the United States. (See, e.g., Kreling D, et al., Prescription Drug Trends: A Chartbook Update, Menlo Park, CA: Kaiser Family Foundation, at 51 (2000)) (Ex. C hereto).

3. The preferred dosage of CEE that Plunkett discloses is 0.600 mg CEE. Page 9 of Applicants' application compares the claimed invention to a combination using 0.625 mg CEE. The difference between the dosages of 0.600 mg CEE and 0.625 mg CEE is not a meaningful difference when compared to Applicants' invention. For purposes of treating or inhibiting vasomotor symptoms, one skilled in the art would consider a daily dosage of 0.600 mg CEE to be clinically equivalent to a dosage of 0.625 mg CEE. Therefore, Applicants provided comparative results of its claimed invention with the preferred dosages of MPA and CEE that Plunkett discloses.

4. The results on page 9 of Applicants' application describe some of the results obtained in the Women's Health, Osteoporosis, Progestin, Estrogen study ("H.O.P.E. study"). Relief of vasomotor symptoms was analyzed in patients who experienced at least an average of 7 to 8 moderate-to-severe hot flushes per day during the 7-day period just prior to the initiation of treatment in this study. The results on page 9 reflect the results of 4 of the 8 regimens used in the H.O.P.E. study administered daily: (1) 0.625 mg CEE plus 2.5 mg MPA ("PREMPRO"); (2) 0.45 mg CEE plus 1.5 mg MPA; (3) 0.3 mg CEE plus 1.5 mg MPA; and (4) a placebo. The first table on page 9 shows the mean number of hot flushes. The second table shows the mean daily severity of the flushes. These results are also shown in Figures 1 and 2.

5. The results on page 9 of Applicants' application show that all doses of CEE plus MPA reduced the mean number and mean severity of hot flushes experienced by the women in the clinical study compared with taking placebo. The mean daily number and mean severity of hot

flushes in the lower dosage groups were not significantly different than the mean number and mean severity of the much higher and commercially available dose combination containing 0.625 mg CEE and 2.5 mg MPA. These results demonstrated that the combinations of 1.5 mg MPA with the lower doses, 0.45 or 0.30 mg, CEE, were as effective in rapidly reducing the number and severity of hot flushes to essentially the much higher and commercially available dose combination containing 0.625 mg CEE and 2.5 mg MPA.

6. The results on page 9 of Applicants' application were contrary to what would have been expected to those skilled in the art. The results surprisingly and unexpectedly demonstrated that all doses of CEE and MPA reduced the number and severity of hot flushes experienced by the women in this study compared with women taking placebo. It was unexpected that providing a daily dosage of 1.5 mg MPA in combination with the lower doses, 0.45 or 0.30 mg, CEE, rapidly reduced the number and severity of hot flushes to the same extent as the much higher and commercially available dose combination containing 0.625 mg CEE and 2.5 mg MPA.

7. The H.O.P.E. study demonstrated that dosages of CEE and MPA may be better than equivalent dosages of unopposed CEE for vasomotor symptom relief. Previous studies with various dosages of CEE showed no additive effect of MPA on vasomotor relief. (See Greendale et al., Obstetrics and Gynecology, 92:982-988 (1998)). Greendale et al. reported studies using the following regimens: (1) placebo; (2) 0.625 mg CEE daily; (3) 0.625 mg CEE daily plus 2.5 mg MPA daily; (4) 0.625 mg CEE daily plus 10 mg MPA for 12 days per month; and (5) 0.625 mg CEE daily plus 200 mg micronized progesterone for 12 days per month. Greendale et al. reported that there was "convincing evidence" that regimens using CEE plus MPA were not more effective than CEE alone against vasomotor symptoms. However, the H.O.P.E. study unexpectedly demonstrated that at the particular low dose of 1.5 mg, MPA may contribute vasomotor relief in combination with the lower dosages of 0.3 or 0.45 mg CEE. These results are

preliminary evidence that there is a therapeutic role for MPA beyond endometrial protection when lower dosages of CEE are used. The H.O.P.E. study surprisingly demonstrated that at these low doses MPA may contribute to ameliorating the vasomotor symptoms.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the patent or any reexamination certificate issued therefor.

Dated: 12/15/03

ROGERIO A. LOBO, M.D.

OBSTETRICS AND GYNECOLOGY CLINICS OF NORTH AMERICA

Primary Care of the Mature Woman

VERONICA A. RAVNIKAR, MD, GUEST EDITOR

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PROGESTINS IN PREVENTIVE HORMONE THERAPY

Including Pharmacology of the New Progestins, Desogestrel, Norgestimate, and Gestodene: Are There Advantages?

Nancy B. Sobel, MD, PhD

HISTORY

The development and characterization of the synthetic progestins used in hormone replacement therapy (HRT) and contraception are an outgrowth of research on the hormonal control of reproduction conducted during the early to middle twentieth century. Progesterone was isolated from the corpus luteum of sows by Corner and Allen in the 1930s. Before this, progesterone had been synthesized commercially from plant (soy beans, yams) and animal (ox bile) sources. It was not until Marker successfully synthesized progesterone from the Mexican yam in the 1940s that large quantities of progesterone became available at a reasonable price. Natural steroids, however, are difficult to control. They are inactive when given orally and highly insoluble in plasma, and therefore, the search for orally active steroids was begun. Originally motivated by the synthesis of cortisone, chemists discovered the progestational activity of 19-norsteroids. In 1951, Djerassi[15] prepared a derivative of 19-nortosterone, norethisterone (known as norethindrone in the United States), which was the first highly effective, orally active progestogen for human use. In subsequent years, attention was focused principally on the potential of progestational agents to control abnormal bleeding, and then as a contraceptive agent, resulting in the first oral agent in the early 1960s.[17, 26, 82]

From the Department of Gynecology, Lahey Clinic, Burlington; and Department of Gynecology, Massachusetts General Hospital, Boston, Massachusetts

PROGESTIN STRUCTURE AND NOMENCLATURE

Steroid hormones are derivatives of cholesterol, a 27-carbon compound, and have a common chemical structure based on the 4-ring perhydrocyclopentanephenanthrene molecule. This is composed of one 5-carbon and three 6-carbon rings lettered A through D and numbered counterclockwise (Fig. 1). The sex steroid hormones are divided into three main groups according to their number of carbon atoms: the 21 carbon (21C) pregnane nucleus, precursor for progestins (and corticoids); the 19C androgen series, based on the androstane nucleus; and 18C estrogen, from the estrane nucleus. Synthetic progestins are also classified into three groups: pregnanes, estranes, and gonanes.

Estranes and their derivatives, the gonanes, are employed predominantly in contraception, and all are derived from norethindrone. Because both groups are characterized by the absence of a methyl group between rings A and B (i.e., C19), they have been designated the 19-nortestosterone progestins or 19-norprogestins (Fig. 2). All the structures are similar, but the "minor" alterations in structure can lead to dramatic differences in biochemical activity. Estranes are characterized by the addition of an ethinyl group at position 17. Differences between estranes involve double-bond position (norethynodrel) and placement of acetate moieties (norethindrone acetate and ethynodiol diacetate). Norgestrel, the first gonane progestin, synthesized from norethindrone by Smith[81] in the early 1960s, is also included in this class.

The gonanes include norgestrel and its biologically active L-isomer, levonorgestrol (LNG). The gonanes are distinguished from the estranes by the addition of a methyl group at position C18 (Fig. 3). In the 1970s and 1980s, efforts were made to minimize the intrinsic androgenicity of the 19-norprogestins. This produced a new generation of progestins, the gonanes desogestrel (Organon, Org 2969), norgestimate (Ortho-Cilag, ORF 10131), and gestodene (Schering AG, SH T 546). Structurally, gestodene differs from LNG only by the presence of a double bond in the D ring between carbons 15 and 16. Desogestrel differs from these by the absence of a keto group at position 3. Norgestimate is LNG with an oxime group at C3 and an additional acetate group at C17.

Another group of progestins, the pregnanes, became available when it was discovered that acetylation of the 17-hydroxy group of 17-hydroxyprogesterone also produced oral potency. Pregnanes, C-21 progestins, are the class of progestins widely used for noncontraceptive applications such as HRT and the treatment of carcinoma. These include medroxyprogesterone acetate (MPA), megestrol acetate, chlormadione acetate, and cyproterone acetate. Each drug has substituents at the 17 and 6 positions. Interestingly, these agents were not used in oral contraceptives (OC) because early studies, later refuted, associated high doses with an increased incidence of carcinoma of the breast in beagle dogs. In fact, only one pregnane-containing OC, Provest, ever reached the US market.[17]

PHARMACODYNAMICS AND SELECTIVITY

On ingestion, oral steroids are absorbed by the small intestines. From there, they are transported by means of the portal system to the liver where they may be modified and circulated systemically or eliminated by biliary excretion. This is referred to as the liver's presystemic or *first-pass* effect. From the gallbladder, molecules are returned to the small bowel, reabsorbed into the portal circulation, or excreted in the feces.[63, 90] Norgestrel does not undergo a first-pass effect,[87] although most other progestins do, resulting in variations in bioavailability among users.

Text continued on page 305

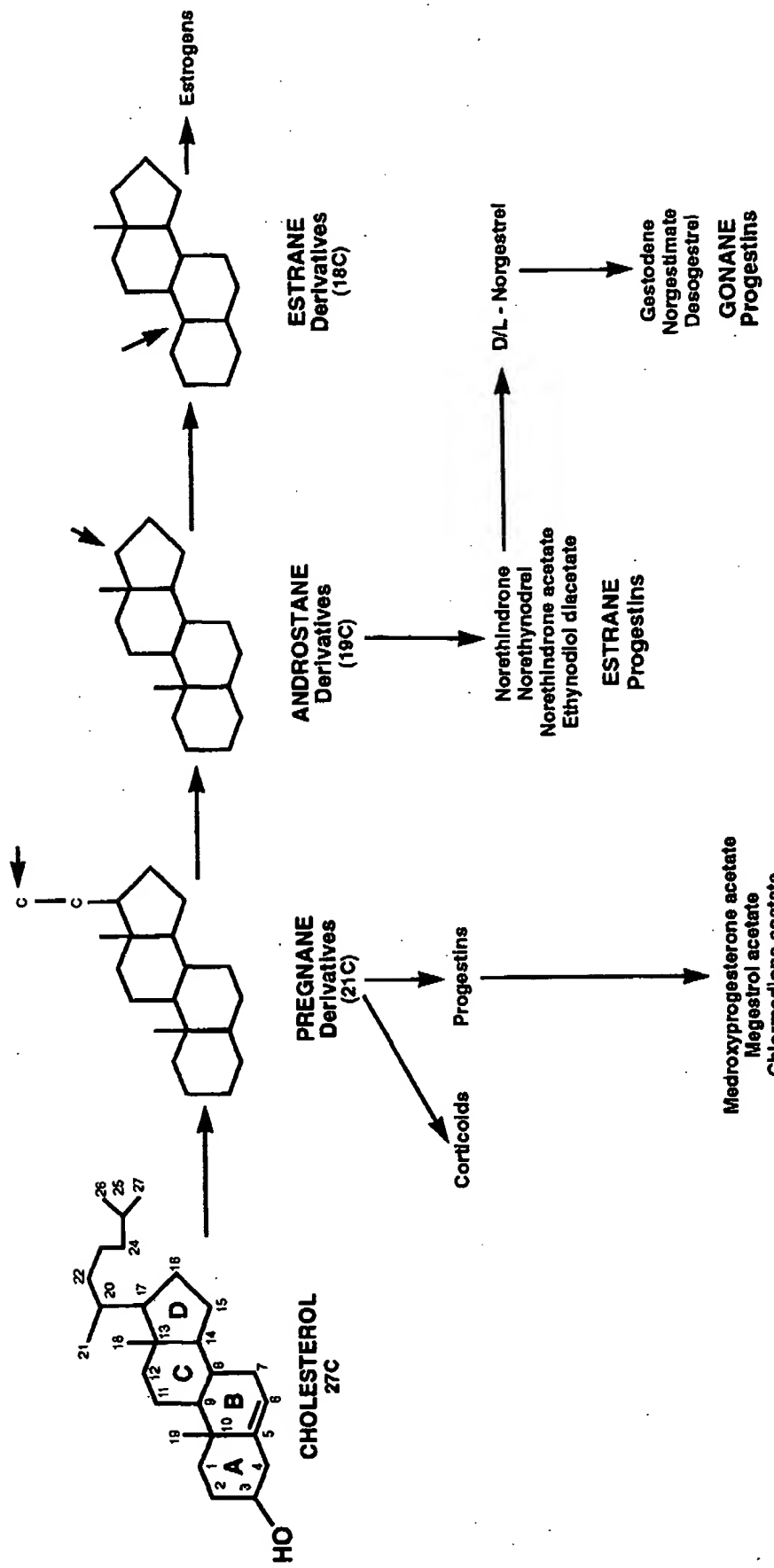

Figure 1. Relationship of synthetic progestins used in hormone replacement therapy.

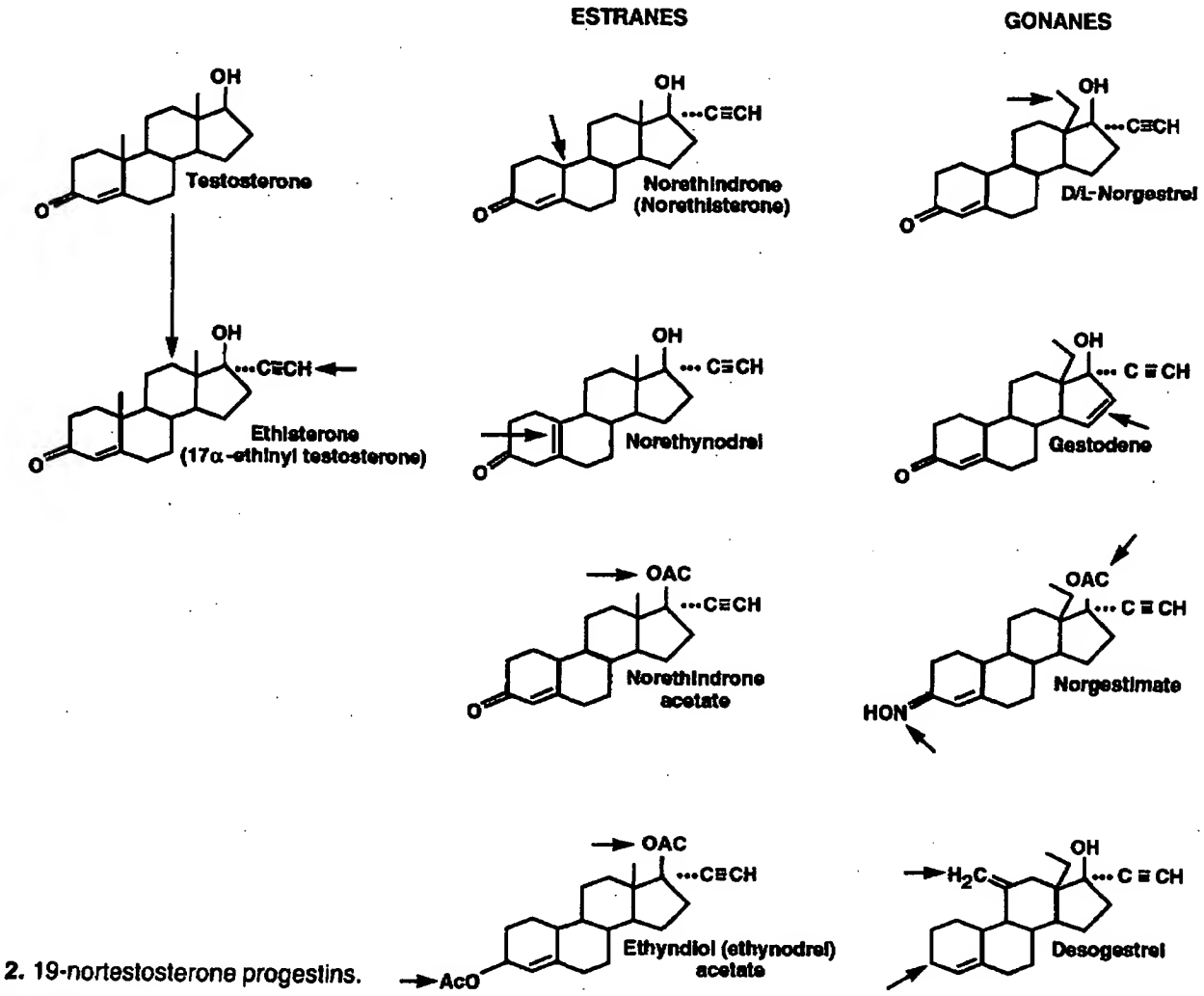

Figure 2. 19-nortestosterone progestins.

Figure 2. 19-nortestosterone progestins.

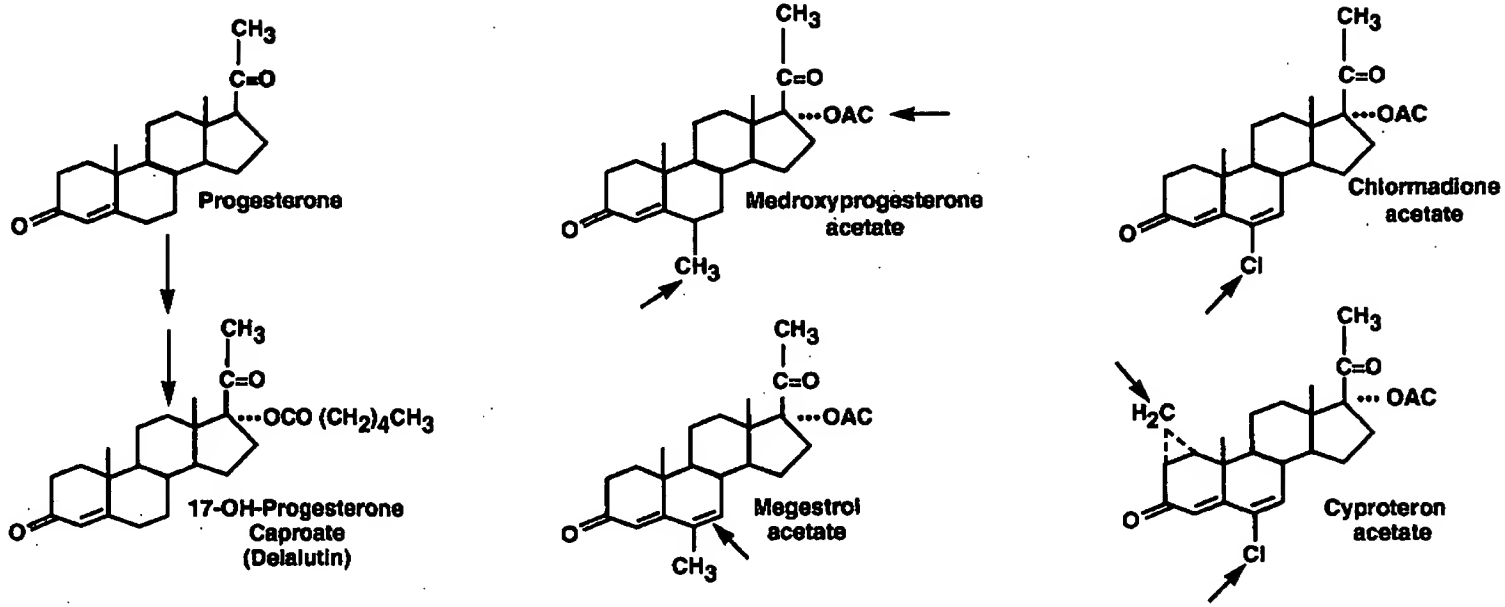

Figure 3. C-21 pregnane progestins.

Figure 4. *See legend on opposite page*

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Each progestin has a different affinity for sex hormone–binding globulin (SHBG) and can modulate the levels of SHBG, as can the estrogens with which they are used. The relationship between estrogen and progestin interactions has variously been described as the simple algebraic sum of their biologic activity (biogebraic),[96] and as a complex interaction between the effects of the estrogen and progestin components. These effects can result in the displacement of different amounts of free testosterone from SHBG, producing variable degrees of androgenicity. Several studies have shown different affinities of the new progestins for SHBG relative to LNG.

The half-lives of progestins range from about 10 hours (oral medroxyprogesterone acetate, megestrol acetate, norethindrone, and desogestrel) to more than 2 days (LNG and norgestimate). Use of compounds with a longer half-life may permit the suppression of gonadotropins during the 7-day placebo phase of the pill[90] and, by corollary, may help alleviate hot flushes when used in sequential HRT. The intramuscular form of MPA, Depo-Provera, has an elimination half-life of about 50 days.

Estranes are converted to norethindrone, although not completely, and thus formulations that use these compounds may lower progestin potency and side effects.[90] Norethynodrel has been noted to have some estrogenic activity on endometrium. Although some investigators believe that this is the result of traces of mestranol left over from the synthetic process, other authors[46] have demonstrated that all the estranes have weak binding to the estrogen receptor protein. Norgestrel exists as a 50:50 racemic mixture, the D-form of which is biologically inactive. Its purified form is levonorgestrel; thus, at any dose, LNG has twice the potency of D/L-norgestrel.

The new gonane progestins, all derivatives of norgestrel, have been used in Europe for more than a decade and were recently introduced into the United States. Desogestrel is converted in two steps into its active metabolite 3-ketodesogestrel[34] (11-methylene LNG). Norgestimate is biologically active as are its metabolites 17-deacetylnorgestimate, D-norgestrel, levonorgestrel, and 3-ketonorgestimate.[60] Gestodene has the highest progestogenic activity of the newer compounds as well as a marked affinity for the aldosterone receptor protein.[18] Oral contraceptive formulations using desogestrel are now the most prescribed in Europe. To date, no United States formulation contains gestodene.

In 1988, following a published assertion[47] that ethinyl estradiol (EE) levels appeared elevated among women using gestodene-containing formulations, an apparent increase in thromboembolism was noted in anecdotal reports of complications to the German government. No increase in phlebitis, however, has been demonstrated clinically with the use of any OC containing the new progestins, gestodene and desogestrel.[44] No association with thrombophlebitis was found in controlled clinical trials with estrogen replacement therapy.[5]

Based on the compilation of data[14, 18, 52, 67, 93] by Dickey,[13] the activities of different oral progestins in animal assays with respect to progestagenic and androgenic effects are shown in Figure 4. In these pharmacologic studies, as well as in many others, gestodene is the most powerful progestin. Gonanes, other than norgestimate, have higher progestagenic activity than estranes in receptor-binding and bioassays (see Fig. 4). Unfortunately, the C18 methylation of the

Figure 4. See legend on opposite page

Figure 4. Biologic activity of selected progestins. Oral activity in different animal assays: black bar = progestin activity, shaded bar = androgen activity. (*Data from* references 13, 14, 18, 52, 67, and 93.)

gonanes accorded increased progestogenic potency but also enhanced the androgenic activity of the molecule.[52] Norethynodrel, as well as the pregnanes, are without androgenic activity in the studies of Phillips,[67] on which Figure 4 is based; although Bergink[3] indicated that the pregnanes, particularly MPA, have small but measurable binding to androgen receptors.

Figure 5 represents progestagenic selectivity calculated from the same compilation of data used in Figure 4. Selectivity is the ratio between the desired and undesired pharmacologic effects, in this case the ratio of progesterone-mediated effects to those of androgen. In theory, this means that, at the therapeutic dose used, the drug has a far greater effect on the system intended to be manipulated than on other systems. Although, using these data, desogestrel is the most selective of the synthetic progestins studied and is marketed by its manufacturer as such, ethynodiol diacetate, the progestin in the OC Demulen is equally selective, although one tenth as potent by weight. Several in vitro receptor-binding preparations show similar trends. Other data from Phillips et al[67] suggested that norgestimate is the most specific of the three new progestins. Kloosterboer,[52] using a different progestin as the reference compound, showed gestodene to be the most selective. It should be cautioned, however, that these results are based on bioassays in different species and tissues (from rabbit endometrium to rat ventral prostate) and, in effect, are evaluating data from "apples and oranges." In addition, activities of the parent compounds, not their active metabolites, were used. Receptor-binding and bioassay data may not extrapolate to humans. Discrepancies may well exist among biochemical, animal, human biologic activity, and clinical spectrum. For example, if all estranes are metabolized to norethindrone, it would be anticipated that they would have identical profiles in vivo. Variables influencing biochemical assays include choice of tissue and species, intact versus fractionated cells, and other incubation conditions. Overall effect may vary by dose, formulation, and combination with estrogen. Currently, it is too early to evaluate whether enhanced selectivity will translate into decreased risk of serious sequelae. No study to date has shown any clinical significance of enhanced selectivity.

CLINICAL EFFECTS

Although progestins are the primary active compound in OCs, estrogen being present for cycle control, progestins play a secondary but important role in HRT. They were added to prevent changes that had been noted with unopposed estrogen administration, allaying the major fear of endometrial carcinoma, which may prevent patients from using HRT.

Steroid hormones are known to affect a myriad of systems. This review concentrates on the benefits for which HRT is most commonly prescribed, endometrial protection, cardiovascular disease, osteoporosis, and vasomotor flushes, and briefly reviews one controversial area, the possible effect on carcinoma of the breast. A comprehensive literature review[29] regarding the risks and benefits and effect on life expectancy of HRT as well as clinical guidelines of the American College of Physicians[30] have recently been published.

Effects on Endometrium

Retrospective studies[80, 106] published in 1975 showed an increase in endometrial hyperplasia and carcinoma in women treated with estrogen alone, which, in most patients, may be prevented by the addition of a progestational agent. The

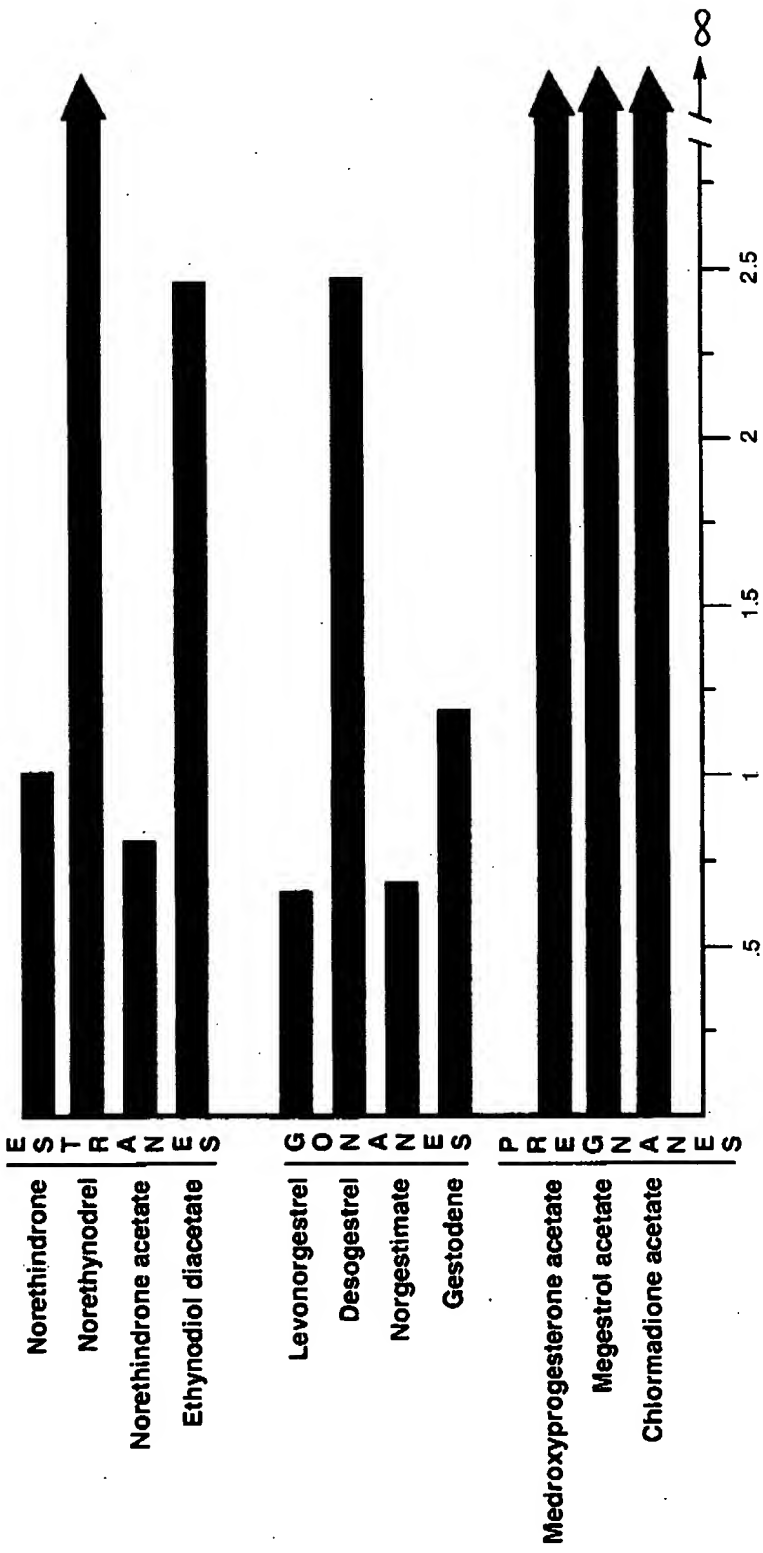

Figure 5. Selectivity of progestin. Ratio of progestin to androgen activity of oral steroids in animal assays. (*Data from* references 13, 14, 18, 52, 67, and 93.)

addition of progestin, as in combined estrogen-progestin therapy, can actually lower the incidence of the development of endometrial hyperplasia[102] and carcinoma.[25] In a 5-year prospective study with 4-year follow-up results, Gambrell et al[25] reported that the incidence of endometrial carcinoma was significantly decreased from 248 out of 100,000 women in the general population to 56 out of 100,000 women, figures that are lower than those in the control group without therapy, thereby making the use of HRT a form of prophylaxis compared with women who do not use HRT. Varma[97] reported that the addition of a progestin for more than 10 days monthly resulted in no evidence of cystic hyperplasia in 392 women. Other authors[7, 25] demonstrated that the addition of a progestin decreased the rate of hyperplasia from more than 20% without progestins to less than 1% if progestins were added for 12 or 13 days. Over time, doses of progestin used in HRT have been decreased without adverse effects on the endometrium. A limit to the beneficial effect has been demonstrated histologically and biochemically at higher doses of norethindrone and norgestrel,[103] possibly because of decreasing levels of estrogen-induced progesterone receptors or enzymes.

Cardiovascular Disease, Lipids, and Lipoproteins

It is predicted that almost 60 million persons, 20% of the US population, will be more than 65 years old in the year 2025. Cardiovascular diseases account for the deaths of over half a million women annually in the United States; more than 50% of these deaths are the result of ischemic heart disease. Dozens of studies have demonstrated an apparent relationship between serum lipoproteins and heart disease. Many of these studies, however, have been performed only in men with the results extrapolated to women, which is unacceptable. Although not all authorities agree that the death rates from arterial disease increase after menopause, other than the increase from premature surgical oophorectomy,[11] a number of studies of different designs, including tens of thousands of women, have shown an apparent 50% to 70% decrease in the risk from coronary heart disease in women taking oral estrogen.[2, 37, 84, 85, 86]

The first observational reports of the benefit of estrogen replacement therapy appeared in two sequential articles in the October 1985 volume of the *New England Journal of Medicine*, presenting data from the Nurses' Health[86] and Framingham studies.[104] The latter study initially proposed an increased risk; however, reanalysis of the data showed a 50% protection against coronary artery disease, bringing the conclusions in line with many other studies published to date.[16] Similar results have been documented more recently with combined (estrogen and progesterone) HRT.[22, 62, 94] Several mechanisms have been postulated to mediate this beneficial impact. These include direct effects on endothelial elements in vessels; secretion of vasoactive peptides leading to vasodilation; a balance between thrombotic and atherogenic mechanisms[71]; and changes in carbohydrate, prostacyclin, or lipoprotein metabolism.[29] Lipid changes seen with HRT may be a benefit of pharmacologic doses rather than being a physiologic effect of "replacing" missing hormones.

The Lipid Research Clinic study[6] concluded that about 30% of cardiovascular risk is due to lipoproteins. Much of the data to date related to the effect of progestins on the cardiovascular system have investigated the impact of lipids and lipoprotein mechanisms.

Lipoproteins are high–molecular weight proteins that transport lipids through the plasma. The polar lipids form a core, predominantly triglycerides in very low-density lipoprotein (VLDL) and cholesterol ester in high-density lipo-

protein (HDL) and low-density lipoprotein (LDL). This core is surrounded by a surface coat of hydrophilic phospholipids, including apoproteins (A-I and A-II in HDL and B-100 in LDL) that help to maintain particle solubility and to direct the lipoproteins to their site of metabolism by binding to cell membrane receptors. During the process that begins with intestinal chylomicron formation, proportionally more triglyceride is removed leaving a higher concentration of cholesterol. In order of increasing density, this leaves VLDL, LDL, and HDL, HDL_3, HDL_{2a}, and HDL_{2b}. Normally as triglycerides are removed, remnants (intermediate-density lipoproteins [IDL]) and LDLs are returned to the liver and taken up by hepatic receptors. Multiple factors, including increased dietary fat, may result in excess levels of circulating remnants in the plasma. Oxidation of IDL and LDL is thought to result in the accumulation of lipids in arterial wall macrophages, initiating atherosclerosis. High-density lipoprotein is thought to play a role in "reverse cholesterol transport" of lipids from cells to the liver for excretion. High-density lipoprotein appears to provide a protective effect,[28] and LDL correlates with an increased risk of heart disease. Estrogens, in general, are thought to increase HDL, triglycerides, and apoprotein B and to lower LDL, partially by decreasing levels of the enzyme hepatic lipase. Walsh et al,[98] in a study using oral estrogens, reported a 15% increase in HDL, a 16% decrease in LDL, and no appreciable advantage of doubling doses except on triglycerides after 3 months. A dose of transdermal estrogen, 0.05 mg, was shown to have no appreciable effect on HDL at 6 weeks,[98] but a significant effect was noted at 24 weeks with the 0.1 mg transdermal patch.[88] Some studies[39, 91, 95] showed the most dramatic effect on women with elevated cholesterol levels or coronary artery disease. The Leisure World study[37] looked at the effect of estrogens on women with previous myocardial infarction or cerebrovascular accident and reported a 50% decrease in risk of dying from subsequent myocardial infarction or cerebrovascular accident. Sullivan[91] evaluated women angiographically and noted that women with the worst coronary artery disease had a better 10-year survival than those not taking estrogen.

Estrogens and progestins, however, sometimes have opposing effects. Early studies[21, 39, 40, 64, 94] suggested that some progestins, particularly the "older" 19-norprogestins, may detrimentally affect cardiovascular risk by lowering HDL and triglycerides and elevating LDL, thereby potentially reversing some of the beneficial effects of estrogen. These studies, however, were often of short duration, small sample size, and used high doses of progestin (10 mg MPA or norethindrone acetate [NETA]). For example, the often-quoted Hirvonen[39] paper had only six patients in each of three study arms. Comparisons of natural progesterone with synthetic progestagens in sequential regimens demonstrated decreased levels of HDL with the synthetic progestagens but no adverse influence of natural progesterone on the beneficial changes in lipids from estrogen,[33, 43, 64] except that HDL was decreased with the 300 mg dose of progesterone.[21] Part of the discrepancies may be caused by the different assays used to measure lipoprotein levels. Estimation of levels of lipoproteins can be influenced by the expertise of the laboratory staff and the biochemical and mathematic techniques employed. For example, the Friedewald[23] formula, which is often used to calculate LDL and VLDL from total cholesterol and HDL, may give different values than when these are estimated using centrifugal density gradients.

Some longer-term studies[97] have shown that these short-term effects on lipids may be reversed over time, possibly because of the induction of enzymes. Since the late 1980s, reports of combined HRT have shown decreases in LDL and total cholesterol levels with modest changes in HDL over 1- to 5-year periods. In some instances, the change in HDL parallels that in estrogen only or placebo controls, and both tend to return to baseline levels after 1 year.[9, 12, 42, 43, 99] With continuous therapy over 5 years using estradiol 2 mg, NETA 1 mg, or a placebo,

Table 1. SUMMARY OF EFFECTS OF PROGESTINS ON LIPOPROTEINS USING COMBINED OR SEQUENTIAL HORMONE REPLACEMENT THERAPY FOR MORE THAN 6 MONTHS

Agent	Dose (mg)	Sequential r Combined	HDL	LDL	TG	TC
Estrogen only			↑	NS/↓	↑	NS
Progestin						
NETA	0.25–1.0	Both	NS/↓	↓	NS	↓
TTS-NETA	0.25	Sequential	NS	↓	↓	↓
		Combined	NS	NS	NS	NS
D/L–NG	0.075–0.5	Sequential	NS/↓	↓	NS/↓	↓
	0.25	Combined	↓	↓	↓	↓
LNG	0.075	Sequential	NS	↓	—	—
MPA	10	Sequential	NS/↓	NS/↓	NS	↓
	5	Both	↑/NS	NS/↓	↑/NS	NS/↓
	2.5	Combined	↑/NS	NS/↓	NS	NS/↓
CPA	1.0	Sequential	NS	↓	NS	↓
Megace	7.5	Sequential	NS	↓	↓	↓
	5	Combined	NS	↓	NS	↓
	2.5	Combined	NS	NS	↑	NS
Micr Prog	200	Both	↑/NS	↓	NS	NS/↓
DSG	0.15	Sequential	↑/NS	↓	NS/↓	NS/↓
		Combined	↓	↓	↓	↓

CPA = cyproterone acetate; D/L-NG = D/L-norgestrel; DSG = desogestrel; HDL = high density lipoproteins; LDL = low density lipoproteins; LNG = levonorgestrel; Micr Prog = micronized progesterone; MPA = medroxyprogesterone acetate; NET = norethindrone; NETA = norethindrone acetate; NS = not significant; TC = total cholesterol; TG = triglycerides; TTS-NET = transdermal norethindrone; ↑ = significant increase; ↓ = significant decrease.

total cholesterol and LDL each were reduced 20% in the HRT group, triglycerides were unchanged, and HDL was reduced in both the treated and control groups.[8]

Table 1 is a summary of available data regarding the effect of combined* and sequential† HRT for greater than 6 months on lipoprotein levels. Other than one report of opposing effects on triglycerides,[12] little difference is seen between oral or transdermal forms of progestin, using either low-dose 19-norprogestins or C-21 pregnane progestins, including MPA, megestrol and cyproterone acetate. Note that the 2.5 and 5 mg doses of MPA, 200 mg dose of micronized progesterone, and the 0.15 mg sequential dose of desogestrel have effects similar to those seen with unopposed estrogen. This may be the result of the lower doses used rather than the specific progestins. However, the decrease in HDL and triglycerides, as well as LDL and total cholesterol, with 0.15 mg of desogestrel in combined HRT[57a] does not support this theory. Cyclic variations continue to be seen in HDL and apo A-I levels between the estrogen only and estrogen-progesterone phases in combined-sequential HRT; these were exaggerated in smokers.[32]

Many researchers and clinicians believe that the new progestins may have important advantages over those now in use, such as fewer changes in lipid metabolism, thereby potentially diminishing the risk of cardiovascular problems. At the present time, no US studies have appeared, and few foreign studies use the new progestins in HRT. Published reports currently are limited to desogestrel. Foreign studies, in general, have few controls and compare fixed HRT combinations in which both estrogens and progestins differ between study arms.

*References 8, 9, 33, 42, 57, 57a, 59, 70, 83, 99, 105, 107.
†References 2, 21, 33, 39, 41, 43, 55, 57, 58, 66, 69, 70, 74, 78, 92, 105.

The majority used sequential regimens of estrogen and MPA 5 mg, NETA 1 mg, LNG 75 μg, or desogestrel 150 μg for 10 days per month and reported significant decreases in LDL and minor or cyclic changes in HDL.[31, 58] Only a report from Israel[92] showed an advantage with the new progestin, desogestrel, compared with sequential doses of MPA and NETA. Over a 9-month period, HDL was calculated to increase 30% with desogestrel, 20% with MPA, and not significantly with NETA. However, NETA was used at a 1-mg dose in combination with estradiol and estriol, whereas conjugated equine estrogens were matched with different durations of desogestrel and MPA use. Low-density lipoprotein decreases were 10% (MPA), 15% (NETA), and 27% (desogestrel). To date, no direct comparison has been made of the effectiveness of the three new progestins other than in OCs in which desogestrel, norgestimate, and gestodene appear to increase triglyceride levels and have no significant effect on LDL or total cholesterol.[73] A recent review[48] shows desogestrel having different effects on lipoproteins when used in OCs increasing HDL and triglycerides and having no significant change in LDL level; one might speculate that these differences are caused by the greater proportion of estrogen in OCs.

Many studies, particularly with continuous HRT, show a decrease in LDL and total cholesterol over time. Three studies,[32, 59, 83] however, demonstrated no significant change in HDL/LDL or total cholesterol/LDL ratios with combined-continuous HRT. Even if both HDL and LDL are reduced, a beneficial effect may occur when the reduction of LDL is greater than that of HDL. Conversely, if studies show the beneficial effect persists in the presence of lipoprotein levels returning to baseline levels, this may imply indirect support of some of the other hypotheses mentioned previously. In addition, it is not yet known whether a statistically significant change in levels will also be clinically significant. A recent observational study has documented that HRT is associated with such a favorable physiologic profile,[62] but further randomized trials are required. The ongoing Women's Health Initiative[11a] may help to answer this question.

Osteoporosis

Osteoporosis affects 15 to 20 million women—half to one third of postmenopausal women. It is estimated to result in 1.3 million fractures annually and to cost 7 to 10 billion dollars a year in the United States. Peak cortical bone density occurs in women at 35 years of age, whereas trabecular density occurs somewhat earlier and decreases rapidly 3 to 7 years after menopause, about 15% every 10 years. Bone mass is affected by a number of additional variables, including age, genetics, calcium, medications, activity, smoking, and coexisting medical conditions.

Absorption of calcium in the gastrointestinal tract appears to be compromised in menopausal women and improved by estrogen replacement. An increase in oral calcium intake, however, is not enough.[72] Estrogen has been documented to increase absorption of calcium in the gastrointestinal tract, decrease bone resorption, and retard postmenopausal bone loss.[27, 36] Estrogen may prevent up to 80% of vertebral compression fractures and 50% to 60% of fractures of the hip and arm. No data are available relating to the effect of estrogen on death rate from hip fracture. A recent report,[22a] however, indicated that at least 7 years of estrogen therapy after menopause are needed for long-term protection of bone mineral density, and even this may not protect women aged 75 years and older.

There is evidence[9, 69] that combined estrogen and progestin therapy prevents postmenopausal bone loss, possibly uncoupling of bone formation and resorp-

tion.[10] Others[19, 43, 57, 58, 76, 89] have shown that various combinations of estrogen and progestins, including the transdermal form of progestins, may lead to increased bone formation. Lee[53] hypothesized that progesterone, not estrogen, is the missing factor in the prevention and treatment of osteoporosis. A few studies[35, 58, 74] (although again of questionable, suboptimal design) that compared desogestrel with the older progestins demonstrated reversal of indexes of bone resorption, decreased bone turnover, and prevention of bone loss. More work is needed to clarify the relationship between the effect of estrogen and progesterone and whether any benefit will be derived from use of the new progestins.

Vasomotor Flushes

Vasomotor flushes ("hot flashes") occur in 85% to 90% of menopausal and postmenopausal women and are the reason many women seek medical assistance during the climacteric. Estrogen has been shown to decrease or eliminate hot flushes. In a randomized, double-blind crossover study, Campbell and Whitehead[7] using estrogen 1.25 mg, showed that hot flushes were substantially reduced and sleep was increased. Schiff et al,[75] using a sleep unit, noted a decrease in sleep latency and an increase in REM sleep during estrogen therapy. Progesterone, however, has also been shown to alleviate vasomotor flushes. In women in whom estrogen but not progestin therapy is contraindicated, two progestins have been found to be efficacious in decreasing or relieving hot flushes: MPA, 10 to 40 mg/day or Depo-Provera, in 1- to 3-month intervals as needed; and megestrol acetate (Megace), 20 to 80 mg/day. Unfortunately, progestins do not provide the beneficial effects of estrogen on genital tissues, and some women experience vaginal dryness and resultant dyspareunia with these medications. No work to date has been published regarding the new progestins and vasomotor flushes. Other, nonsteroidal, methods for relief of flushes have been reviewed by Miller.[61]

Carcinoma of the Breast and Hormone Replacement Therapy

Many women fear carcinoma of the breast far more than heart disease or osteoporosis, although the risk of death from cardiovascular disease is about 10 times greater. Some women decline the use of HRT and hormonal contraception despite the lack of current data clearly demonstrating that estrogens or progestins affect the risk of developing breast carcinoma, a risk that increases linearly with age in all women. A variety of studies have been performed to try to elucidate the relationship between sex steroids and carcinoma of the breast. For many years, it was assumed that the breast, like the endometrium, would respond to progesterone stimulation with a protective effect. But biochemical differences in response to progesterone stimulation have been demonstrated[102] between these two tissues. To date, more than 40 studies in the English literature have investigated the question of HRT with and without progestins and breast carcinoma without a clear consensus. Data from Gambrell et al[24] appear to document a protective effect of progesterone with respect to cancer. Two Scandinavian reports[4, 20] suggest the converse. Several large studies show no increased risk. Therefore, until such a positive relationship is more clearly documented, many authorities[39, 100] recommend using estrogen-only HRT in women who have undergone hysterectomy in view of the potential detrimental effects of progestins on cardiovascular risk.

DOSE RECOMMENDATIONS

Hormone replacement therapy currently is prescribed both sequentially and continuously. The classic sequential method attempts to simulate the hormone pattern of premenopausal women and produces a secretory endometrium. Most regimens combine 10 to 14 days of a progestin with 25 days of estrogen per month, although no additional risk of endometrial hyperplasia was demonstrated by combining daily estrogen with cyclic MPA.[33] Using endometrial biopsies, Padwick and colleagues[65] documented that a 5-mg dose of progesterone may be used safely. Women who bleed before day 10 of progestin administration often require a higher dose in subsequent cycles to produce full conversion to a secretory endometrium.[65] Unfortunately, a large number of women experience withdrawal bleeding well into their 60s with the sequential combination.

Recently, the so-called continuous-combined method that involves a constant daily dose of both estrogen and progestin has come into vogue. Its primary advantages include the use of a lower daily dose of progestin, which potentially results in fewer adverse metabolic changes and side effects; these include the dysphoric effects on mood[77] noted with some preparations, as well as breast tenderness, bloating, and headache. In addition, these regimens eventually produce amenorrhea from an atrophic endometrium. On the negative side, however, up to 80% of women experience breakthrough bleeding in the first 6 months and 10% at 12 months. The bleeding in both this and the classic sequential HRT method often results in a major problem with compliance.

Standard estrogen doses, with both sequential and combined regimens, include conjugated (0.625 mg), micronized (1 to 2 mg), or transdermal (0.05 mg) estrogen. In many instances, current doses of progestin in HRT are similar to those in OC preparations. Although equivalent potencies of oral progestins on estrogen-primed endometrium were shown by King and Whitehead[50] to be 5 mg of medroxyprogesterone, 0.35 mg norethindrone, 0.075 mg of D/L-norgestrel, and 200 mg micronized progesterone, the standard dosages of progestins in the sequential regimens usually are 5 to 10 mg of medroxyprogesterone acetate (Provera, Cycrin, Amen), 0.075 mg D/L-norgestrel (Ovrette), 2.5 to 5 mg norethindrone (Micronor, Norlutin, NorQD), 5 to 10 mg norethindrone acetate (Norlutate, Aygestin), 150 μg desogestrel, or 200 mg of micronized oral progesterone daily for 10 to 14 days. Daily continuous combinations usually involve MPA 2.5 to 5 mg, norethindrone 0.35 to 2.1 mg, norethindrone acetate 1 mg, or desogestrel 150 μg/day. Alternate treatments include 250 μg/day of levonorgestrel (Norplant) or Depo-Provera every second or third month to decrease withdrawal bleeding. The longer-term effects on endometrium with these regimens are not yet clear. All of the new progestins are dosed lower than most other commonly used progestins. As mentioned previously, desogestrel has been used at 150 μg daily in both continuous and sequential regimens. Norgestimate has been used effectively in European OCs at daily doses as low as 250 μg and gestodene at 75 μg. Studies being conducted with considerably lower doses may show them to be equally efficacious in HRT with lowered effects on lipids. When it is necessary to use unopposed estrogen, endometrial sampling has been recommended annually or when the endometrial stripe becomes greater than 4 to 8 mm on transvaginal ultrasonography.[54] Archer et al[1] have reported that pretreatment biopsy is unjustified in asymptomatic women with a less than 0.75% yield of cancer or atypia.

ON THE HORIZON

To improve convenience and compliance, many parenteral combinations of steroids have been postulated, some of which are being tested. These include

injectable suspensions and microspheres, transdermal patches combining estrogen and progestagens,[49,55,56,102] subdermal implants, such as the Norplant system, and some biodegradable varieties of implants and pellets. Vaginal rings, when investigated for contraceptive use, produced satisfactory blood levels of hormones.[91] Use of progesterone intrauterine devices, which release 65 mg progesterone daily,[79] have been described for the prevention of endometrial hyperplasia in postmenopausal women.

CONCLUSION

The first hormonal contraceptive combination, introduced in 1960, contained mestranol 150 μg, and norethynodrel 10 mg. Both contraceptive and hormone replacement doses have dropped more than 90% in the intervening years. The current ratio of progestin to estrogen dose in OCs by weight covers a range of more than tenfold, from less than 5 to 50. The biologic activity of the estrogens in OCs, now predominantly ethenyl estradiol, has been shown to be many times that of the estrogens used in HRT. Accordingly, the potential exists for progestin doses in HRT to be decreased even further in the future with the possibility of additional reduction in adverse effects. It is too early to see whether the new progestins will offer any clinical advantages over older compounds. Current data do not uniformly support this concept. Conversely, an optimal combination of estrogen and progestins for prevention of osteoporosis has not yet been determined, nor has a consensus been reached about the effect of steroid hormones on carcinoma of the breast. Therefore, the optimal regimen and route of HRT await the results of future studies.

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Treatment of the Postmenopausal Woman

Basic and Clinical Aspects

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CHAPTER 9

Hot Flashes

Fredi Kronenberg

Hot flashes are the classic sign of menopause as well as the predominant complaint of perimenopausal and menopausal women in the United States, yet it was not until 1975 that serious scientific study of hot flashes was undertaken. In that year, a paper on the measurement of physiological changes during hot flashes demonstrated their objective existence (1), and the phenomenon could no longer be dismissed as being "all in the head," as it often had been previously.

A hot flash is a sudden, transient sensation ranging from warmth to intense heat that spreads over the body, particularly on the chest, face, and head, typically accompanied by flushing, perspiration, and often followed by a chill. In some instances, there are palpitations and a feeling of anxiety. Although these are characteristic features of a hot flash that make it an identifiable phenomenon, the magnitude and duration of any of these components can vary both within and among individuals, and not everyone experiences all of them. So some women flush, others do not; some sweat profusely, others hardly at all. Descriptions of hot flashes may also include pressure in the head or chest, a burning sensation, nausea, feelings of suffocation, and the inability to concentrate. Thus, just as the 28-day menstrual cycle is seen more in textbooks than in women, women's experiences of hot flashes are more variable than most textbook definitions.

Whether referred to as hot flashes, hot flushes, night sweats, or vasomotor symptoms (terms that are often used interchangeably), these episodic events can disrupt women's sense of well-being and can create problems for professional and social life.

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EPIDEMIOLOGY

Hot flashes primarily affect women who are in the transition to menopause or have become menopausal, whether naturally or due to medical intervention such as ovariectomy, chemotherapy, radiation, or medications that cause estrogen levels to fall. At other stages of the female reproductive life cycle, however, some women describe symptoms very similar to the hot flashes of menopause. A small percentage of premenopausal women report having hot flashes, as do women during pregnancy or in the early postpartum period.

Hot flashes may also be experienced by men upon abrupt loss of testicular function such as occurs following orchiectomy for prostatic or testicular cancer, following certain surgical procedures that compromise testicular function (2–5), or upon administration of GnRH agonists, which result in a fall in testosterone levels (6,7). Men who are hypogonadal due to other causes also can experience hot flashes (4).

Until relatively recently, most of the epidemiological studies of menopause had been conducted in North America and Europe (8–13). These studies found that the majority of women had at least some hot flashes. The prevalence of hot flashes is highest in the first two postmenopausal years, ranging from 58% to 93% in these studies, and lessens over time. In perimenopausal women, reports of hot flash prevalence range from 28% to 65%, and in premenopausal women, from 6% to 63%. Women with surgically induced menopause, at least for the first year postovariectomy, tend to have a relatively high prevalence of hot flashes, comparable to that of women in the first two years of natural menopause (see Tables 1 and 2 of ref. 14 for details of specific studies).

Hot flashes, although frequently occurring with menopause, are not universally experienced. Studies of menopause are now underway in countries around the world, and the data available thus far suggest that

the high prevalence of hot flashes in Western societies is not the experience everywhere. Hot flashes have been reported in many cultures, including Indian, African, Native American, Japanese, Indonesian, Mexican American, Mayan, Thai, Filipino, and Chinese (15–24). But the prevalence of hot flashes within these cultures varies widely. Thus far, the most extensively studied non-Western group has been Japanese women, who report very few hot flashes (18,25). Mayan women in Yucatan, Mexico, do not report any symptoms at menopause other than menstrual cycle irregularity (21). These studies raise interesting questions. Are the physiological changes that are so characteristic of hot flashes in American women truly absent in other groups? Are they present but perceived differently? Are they, perhaps, not attributed to menopause? If absent or experienced by only a small percentage of the population, could this be due to diet, exercise patterns, or other cultural differences? Current research efforts may soon provide answers to some of these questions, and the results may generate leads to new methods of treatment. Increasingly, the patients in a medical practice come from a wide variety of cultural and religious backgrounds. It is therefore necessary to be aware of the menopausal symptoms that may be seen among women of other cultures, as well as to be sensitive to various cultural and medical traditions that might preclude a particular approach to treatment of hot flashes or include treatments not used by Western physicians.

NATURAL HISTORY OF HOT FLASHES

The initial form of hot flashes and their pattern over time differ among women, but the physiological basis for these differences in hot flash patterns and presentations has yet to be definitively explained. For some women, hot flashes begin as menstrual cycles are becoming irregular: they tend to occur when menstrual cycles are absent and disappear when menstrual cycles resume. For others, hot flashes begin when menstrual cycles are still regular, which may be well before menopause. There are also instances in which hot flashes first begin several years after menopause (14). Few investigators have asked about the age and menstrual cycle status at which hot flashes begin, but those who have asked report that for a majority of women hot flashes begin prior to menopause (12,14,26).

The frequency, intensity, and duration of individual hot flash episodes vary both within and among individuals. Hot flashes may occur once a month or as often as every half hour. Most women with hot flashes have them infrequently, but about 10% to 15% of women have very frequent, severe hot flashes (14). Women with frequent hot flashes often have relatively consistent patterns of hot flashes, at least in the short-term. Over months or years, however, an individual's hot flash pattern may change. In many cases hot flashes first occur at night and eventually occur during the day as well. Generally, hot flashes tend to become less frequent over time; however, for some women, they continue at frequent intervals until well into old age (14,27). The intensity of hot flashes can range from mild to very intense, over the course of one day, from day to day, or in different seasons. An individual hot flash episode typically lasts 3 to 6 min, although it can be of shorter duration, and on occasion a hot flash can last for more than 30 min.

The period of time over which hot flashes are most often experienced is 6 months to 2 years; however, women can have hot flashes for 10, 20, or even 40 years (14,26,28). Adequate data on the natural course of hot flashes is lacking because most investigators have not asked women across the life cycle whether they are having hot flashes. Most often excluded are women in their seventies and eighties; it had been assumed, incorrectly, that they would no longer have been experiencing hot flashes.

Although hot flashes often occur spontaneously with no observable trigger (particularly during sleep), some women report specific precipitating factors for their hot flashes. Psychological stress is often cited, as are hot weather (particularly hot, humid weather), a confining space, caffeine, alcohol, and spicy foods (14,29,30).

Few studies have examined factors that might predispose women to hot flashes. No significant association has been found between the occurrence of hot flashes and sociodemographic variables such as employment status, social class, age, or marital status (13). Women with hot flashes are not distinguishable from those without hot flashes by age at menarche, number of pregnancies, or previous medical problems (31). One factor that has been shown to relate to the occurrence of hot flashes in menopausal women is mean body weight and percent ideal body weight. Asymptomatic women had significantly higher mean body weight, percent ideal body, and total circulating estrogen levels, than women with hot flashes (32). Recent data from a prospective study of the natural menopausal transition indicate that women with longer perimenopausal periods were more likely to report hot flashes than were those with a short perimenopausal period (51% as compared with 39%) (33). Further research will determine whether factors such as genetics, diet, and exercise will be found to influence hot flashes.

PHYSIOLOGY OF HOT FLASHES

Thermoregulatory and cardiovascular changes that accompany a hot flash are now well documented.

Characteristic patterns exist amid a range of individual variability (Fig. 1, Table 1). Knowledge of the time sequence of physiological changes during a hot flash has grown incrementally as researchers have measured additional parameters. It is now frequently reported that many women have a premonition of an impending hot flash (an aura), which they distinguish from the hot flash itself. This prodromal feeling is often described as one of disease, anxiety, a tingling sensation, or pressure in the head (14). During this period immediately prior to the onset of a hot flash (approximately 5 to 60 sec), heart rate and cutaneous blood flow begin to increase (34,35).

At the start of a hot flash typically there is a sudden onset of sweating primarily on the upper body but measurable all over the body, as indicated by a rapid drop in skin resistance (increase in skin conductance) (35,36). The main sensation is one of intense heat, although internal body temperature never rises above normal. As cutaneous blood flow increases (34,35) and heart rate continues to accelerate (4 to 35 beats/min) (34,35,37), skin temperature rises, particularly that of the fingers and toes (1 to 7°C) (1,35,38,39), and sweating continues. Evaporative cooling may cause the temperature of the wet skin to drop, particularly on the chest and forehead, where sweating tends to be profuse (35). Heart rate and skin blood flow peak within about 3 min of hot flash onset (34,35). To relieve their discomfort, women initiate a variety of behavioral measures to dissipate heat. The vasodilation, sweating, and behavioral responses result in heat loss and a drop in internal temperature (0.1 to 0.9°C), which reaches a nadir about 5 to 9 min after the onset of the hot flash (35,36). If there has been significant heat loss and core temperature has dropped, there may be the sensation of a chill, or even some shivering as the hot flash resolves. Vasoconstriction, behavior to promote warming, and at times an increase in metabolic rate due to shivering, facilitate the return of body temperature to normal. Skin temperature gradually declines to its pre-hot-flash level. This can take 30 min or more, depending on skin and ambient temperatures. No change in blood pressure has been found in association with a hot flash (34,37,40). Although sweating and the

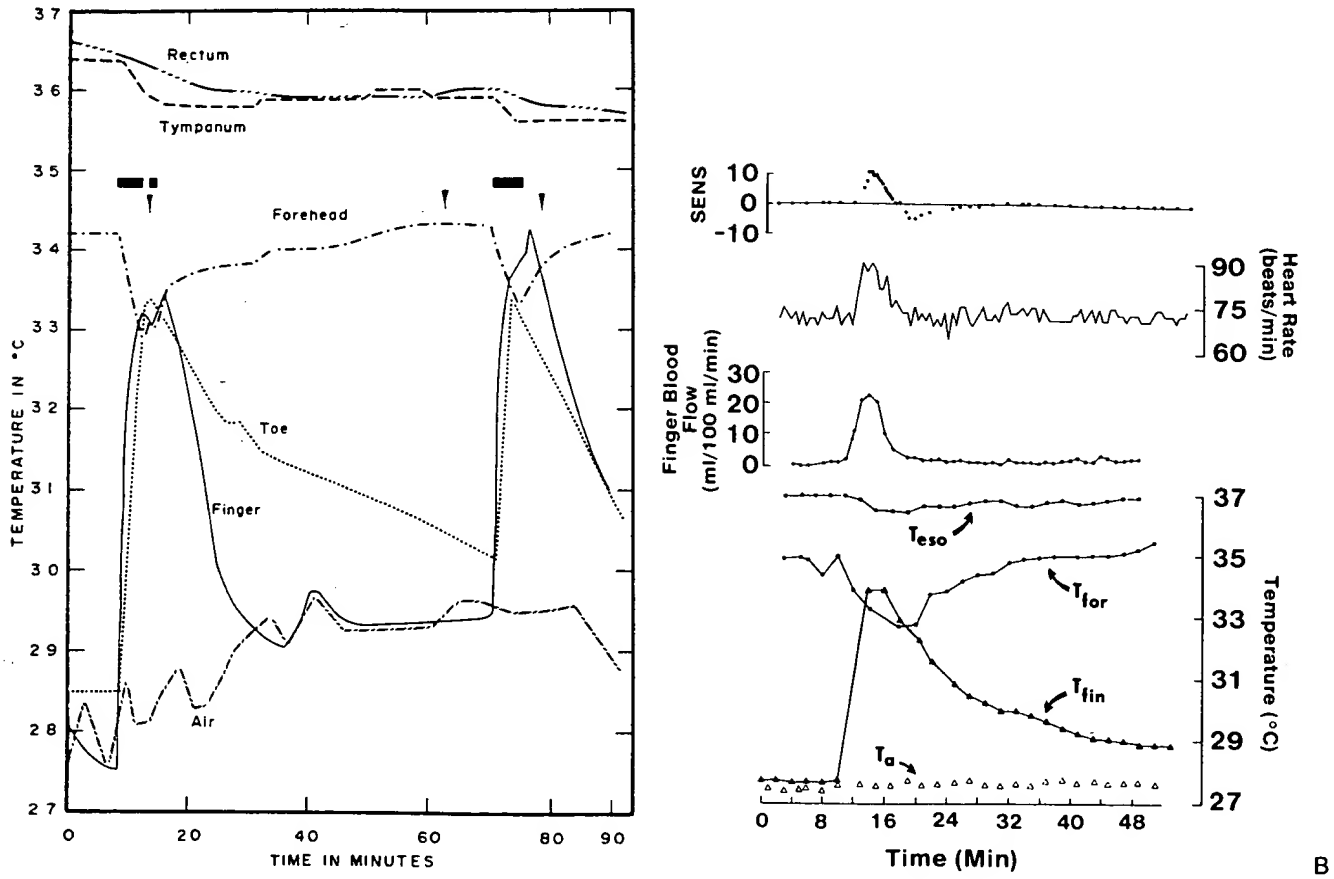

FIG. 1. A: Temperature responses to two spontaneous flashes (■) and evoked flash (■). ↓, Finger stab for blood sample. Nude. (From ref. 1, with permission.) **B:** Thermoregulatory and cardiovascular changes during a typical hot flash at an ambient temperature of 28°C. Subjective sensation, blood flow (finger), heart rate (30-sec averages), skin resistance (chest), internal body temperature (vagina), and skin temperatures (forehead, finger) are depicted. (From ref. 14, with permission.)

TABLE 1. *Clinical picture of a hot flash*

Symptom	Description
Sensation	Sudden feeling of heat and sometimes anxiety
Heart rate	Increases (5–35 bpm), sometimes felt as palpitations
Cutaneous blood flow	Increases; observed as flushing
Finger skin temperature	Rises rapidly (1–7°C) and slowly declines after hot flash ends
Sweating	Often profuse, with rapid onset; rate of evaporation depends on ambient humidity and temperature
Core temperature	Decreases (0.1–0.9°C) several minutes after hot flash starts; sometimes felt as a chill at end of hot flash
Sleeping problems	Increase in nighttime awakenings associated with hot flashes (night sweats)

perception of heat are most intense on the upper body, the temperature of the toes increases concomitantly with finger temperature, and sweating may occur over the lower body as well (1,35), demonstrating that a hot flash is a generalized physiological phenomenon.

The subjective perception of the intensity of a hot flash is likely due to a combination of factors, including the associated sweating and increased heart rate, and probably involves other ill-defined sensations. The sensation of hot flash intensity is not a direct function of absolute skin temperature or the change in skin temperature during a hot flash, since the degree to which finger skin temperature increases during a hot flash is inversely proportional to the baseline skin temperature before the hot flash (Fig. 2) (35,36,41). The more distal the site, the lower skin temperature is likely to be initially and, therefore, the greater the potential for seeing an appreciable rise in skin temperature during a hot flash. As a result, in many studies finger temperature is used as an objective indication of a hot flash. This measurement works well in cool ambient temperature, but less well in warm ambient temperatures when baseline skin temperature already may be high.

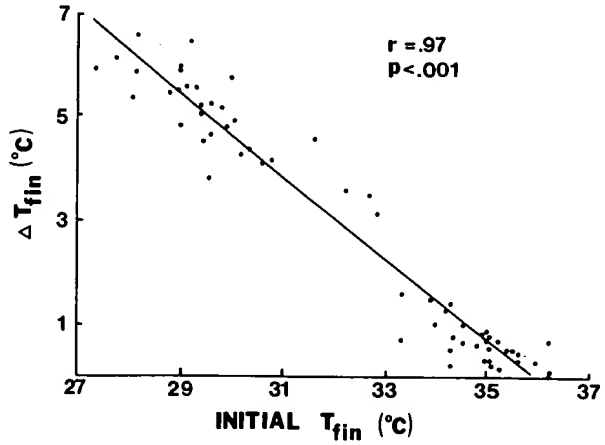

FIG. 2. Relationship between the maximum increase in finger temperature (T_{fin}) during a hot flash and the finger temperature immediately before the hot flash (INITIAL T_{fin}). (From ref. 85, with permission.)

ENDOCRINOLOGY OF HOT FLASHES

Estrogen

Given the long-known association of hot flashes with the onset of menopause and of menopause with a drop in circulating levels of estrogen, investigators have sought to determine whether there might be a relationship between estrogen and hot flashes. In early studies, no correlation was found between estrogen levels in the blood and the presence or absence of hot flashes in postmenopausal women (42–45), nor were any acute changes in estradiol or estrone associated with individual hot flashes (46). In other studies, postmenopausal women with severe hot flashes were found to have lower levels of circulating estrone and estradiol than did asymptomatic women (Fig. 3) (32,47,48). More specifically, Erlik et al. (32) found the fraction of estradiol not bound to sex hormone-binding globulin (SHBG) to be significantly higher in asymptomatic women than in women with hot flashes. Although estrogen does not appear to trigger individual hot flashes, levels of plasma estrogens do play some, as yet undetermined, role in the etiology of hot flashes.

Hot flashes involve more than just the presence of low plasma estrogen levels. Throughout the postmenopausal period, estrogen levels remain low, yet some women never have hot flashes, while for others, hot flashes may occur only sporadically or may soon cease. In other situations in which estrogen levels are low, such as in prepubertal girls or women with anorexia nervosa, hot flashes are not reported. Furthermore, hot flash-like episodes are reported during pregnancy (particularly the last trimester), when plasma estrogen level becomes particularly high (F. Kronenberg, *unpublished data*). Hot flashes also occur in premenopausal women during pituitary suppression with a gonadotropin-releasing hormone (GnRH) agonist, when serum estradiol concentration is maintained at premenopausal levels (49).

What seems to be more important than levels of es-

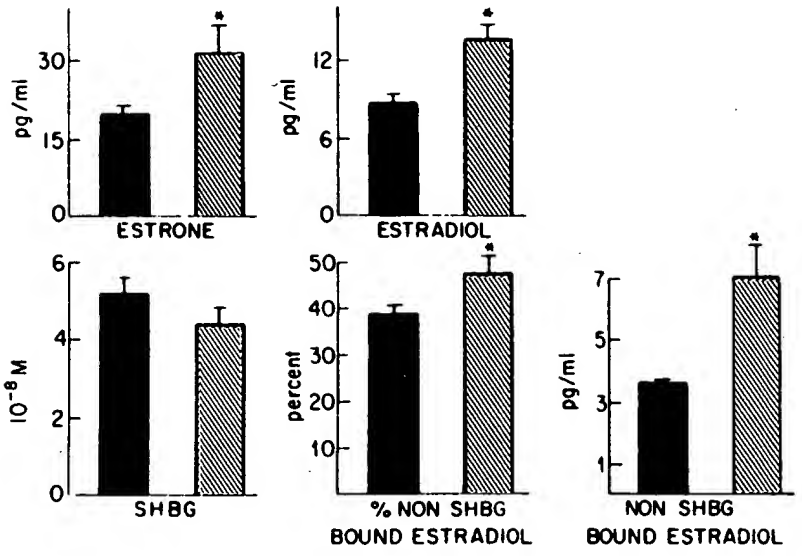

FIG. 3. Mean ± SE levels of estrone, estradiol, sex hormone-binding globulin (SHBG), percent non-SHBG-bound estradiol, and non-SHBG-bound estradiol in 24 women with hot flashes (*solid bars*) compared with 24 asymptomatic subjects (*striped bars*). Asterisk indicates significantly different from asymptomatic subjects. (From ref. 32, with permission.)

trogen per se is a drop in estrogen concentration. For example, the abrupt onset of hot flashes following ovariectomy (42,50) or the administration of GnRH analogues, which cause plasma estrogen to fall (51,52), support this contention. So does the observation that postmenopausal women with gonadal dysgenesis (Turner's syndrome) who have never had normal adult estrogen levels do not experience hot flashes unless they are first prescribed, and then withdrawn from, estrogen (38,53). Estrogen therapy generally ameliorates hot flashes, and upon discontinuation of estrogen treatment, they often return. There have been no reports to indicate whether women with hot flashes have a more precipitous natural decline in estrogen than do those who never have hot flashes.

Hot flashes have also been reported by men upon acute withdrawal of testosterone, such as after total orchiectomy (2,3). The decline in testosterone as men age is far more gradual than the decline in estrogen that occurs in women, which may be the reason that hot flashes are not frequently reported in men. Thus a sudden decrease in sex steroids in either women or men can precipitate hot flashes.

The specific role of estrogen in the etiology of hot flashes remains to be fully understood. In addition to its effect on reproductive tissues, estrogen influences thermoregulatory, neural, and vascular functioning. The firing rate of thermosensitive neurons in the preoptic area of the hypothalamus in response to thermal stimuli can be modulated by estrogen (54). Estrogen also influences internal body temperature, although the direction of the effect differs between studies (55,56). The responsiveness of vascular smooth muscle to vasoactive substances such as epinephrine and norepinephrine is affected by estrogen (57) and has been shown to be greater in women with hot flashes than those without hot flashes (58). Thus estrogen may have peripheral as well as central effects that are important to hot flash physiology.

Luteinizing Hormone (LH)

In addition to the study of estrogen's relationship to hot flashes, the role of gonadotropins has been examined as well, since gonadotropin levels become elevated at menopause. However, high gonadotropin levels are not the direct cause of hot flashes, since (a) LH level remains high postmenopausally while hot flashes tend to lessen, (b) no differences in absolute levels of LH have been found between women with and without hot flashes (59), and (c) hot flashes can be diminished by estrogen doses insufficient to reduce LH levels in the blood (60). Furthermore, when anti-gonadotropins such as danazol or GnRH analogues are given to women with endometriosis, hot flashes often occur despite a decline in LH level (60).

Thus absolute LH level has provided little insight into hot flash etiology. When serial blood samples were drawn, however, LH in the peripheral circulation was found to exhibit a temporal correlation with hot flashes (Fig. 4); most hot flashes are accompanied by an increase in LH (38,39). The correspondence of LH pulses with hot flashes led to speculation that LH might be responsible for the initiation of hot flashes. But it was soon evident that a pulse of LH was not a necessary concomitant of hot flashes. Hot flashes can occur in women who have no episodic LH release such as those with hypophysectomy (Fig. 5) (61,62), in pre- or postmenopausal women in whom pulsatile LH release has been suppressed by treatment with a GnRH agonist (Fig. 6) (51,63,64), and in women with pituitary insufficiency and hypoestrogenism (62). Ravnikar et al. (65) found there to be a similar number of LH

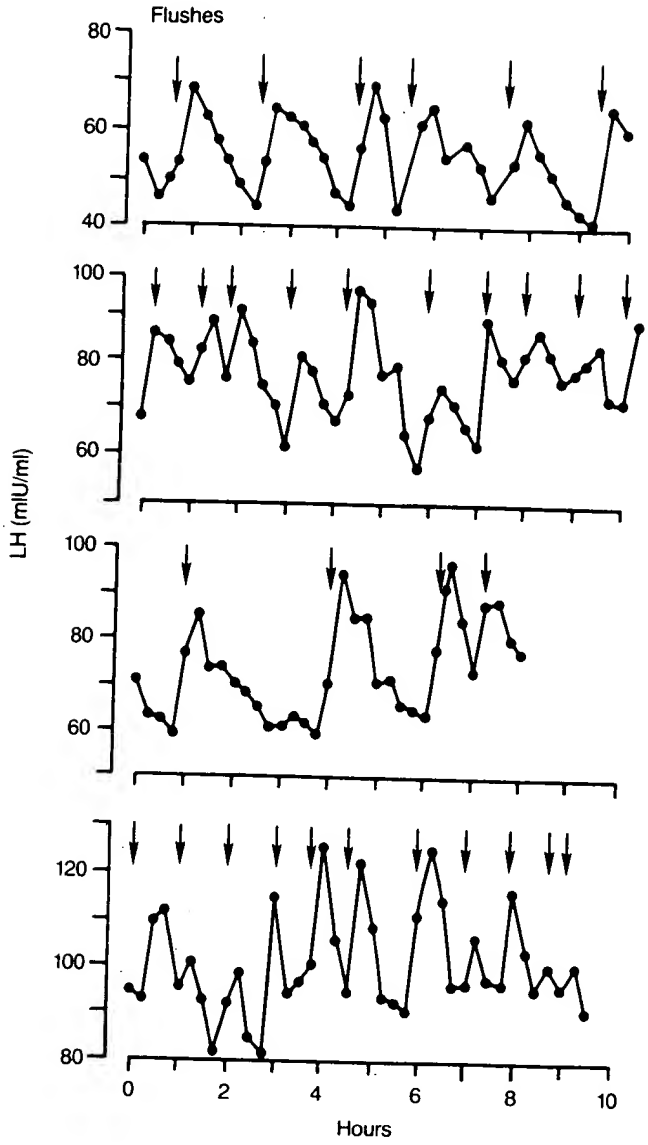

FIG. 4. Pattern of pulsatile LH release and associated menopausal flush episodes. *Arrows* indicate flush onset. Each part illustrates a separate 8- to 10-hr study in which blood samples were obtained at 15-min intervals. Note that each flush is synchronized with an LH pulse. (From ref. 38, with permission.)

pulses in women with or without hot flashes. Thus LH secretion per se is not the immediate trigger of hot flashes.

Gonadotropin-Releasing Hormone (GnRH)

Since pulses of LH were not directly responsible for initiating hot flashes, but they were associated with hot flashes, it was thought that perhaps hot flashes might be initiated at the hypothalamic level and involve the releasing factor for LH. Immunoreactive GnRH was measured in the peripheral circulation of women with and without hot flashes and discovered to be elevated prior to the LH pulses observed with hot flashes. Women with hot flashes also had higher mean plasma immunoreactive GnRH levels than did asymptomatic women (65). Yet women with defects in GnRH synthesis or release (isolated gonadotropin deficiency), who received estrogen treatment, had hot flashes when they were withdrawn from estrogen (66). Furthermore, when GnRH receptors were blocked with a long-acting GnRH antagonist in women who never had hot flashes, although LH pulses were abolished, these women experienced hot flashes for the first time (51). Thus episodic GnRH release is not necessary for hot flashes to occur.

Other Endocrine Studies

Circulating epinephrine and norepinephrine have been measured during hot flashes by several investigators with conflicting results. Casper et al. (38) found no change in epinephrine or norepinephrine in association with individual hot flashes. Given the 2- to-3-min half-life of epinephrine and norepinephrine (67), Kronenberg et al. (35) sampled at more frequent intervals and found a significant increase in plasma epinephrine and a decrease in norepinephrine during hot flashes (Fig. 7). Mashchak et al. (68) found epinephrine to increase but saw no change in norepinephrine levels.

Other substances that have been measured in the peripheral circulation during hot flashes are listed in Table 2. Circulating β-endorphin, β-lipotropin, and adrenocorticotropic hormone (ACTH) increase in association with hot flashes (Fig. 8) (69,70), as do cortisol, dehydroepiandrosterone (DHEA), and androstenedione (46,69,70) (Fig. 9). The peak levels of most of these substances are reached after the subjective hot flash has ended. Prolactin level did not change during hot flashes. Once again, no causal relationships have been found.

HOT FLASHES AND SLEEP

One of the primary complaints of women with hot flashes is that their sleep is disrupted. They may awaken several times during the night, drenched in sweat, necessitating a change of bedding and clothes. Erlik and co-workers (71) used electroencephalography (EEG) to demonstrate that nocturnal awakenings in postmenopausal women with hot flashes were correlated with the occurrence of the hot flashes (Fig. 10). Sleep efficiency is lower and latency to REM (rapid eye movement) sleep is longer in women with hot flashes compared to those with no hot flashes (72). This disturbed sleep often leads to fatigue and irritability during the day. The frequency of awakenings and

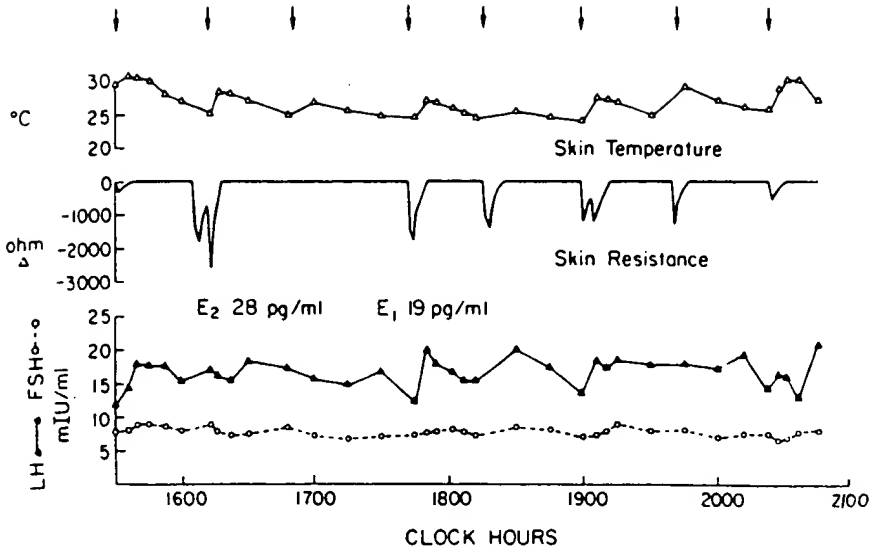

FIG. 5. Serial measurements of skin temperature, skin resistance, and serum LH and FSH levels in a woman after hypophysectomy (patient 1). Skin resistance changes are depicted at 1-min intervals as the change in ohms from the baseline immediately preceding the episode. *Arrows* mark the onsets of subjective hot flushes. E_2, estradiol; E_1, estrone. (From ref. 62, with permission.)

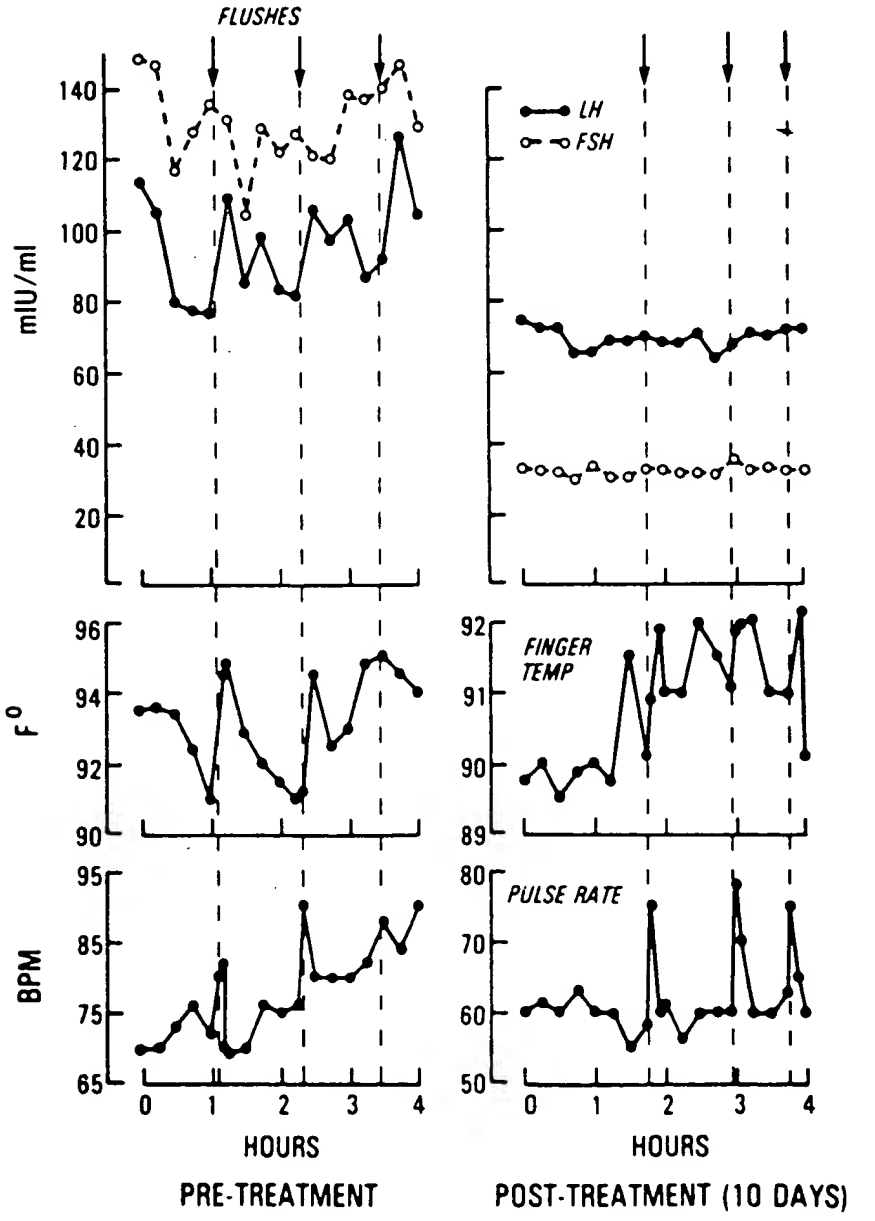

FIG. 6. Changes in finger temperature (°F) and pulse rate (beats/min) in association with flush episodes (*arrows*) and serum concentrations of LH (--) and FSH (O--O) in a representative study of one hypogonadal subject before and after 10 days of daily LRF-Ag administration (50 μg sc). (From ref. 63, with permission.)

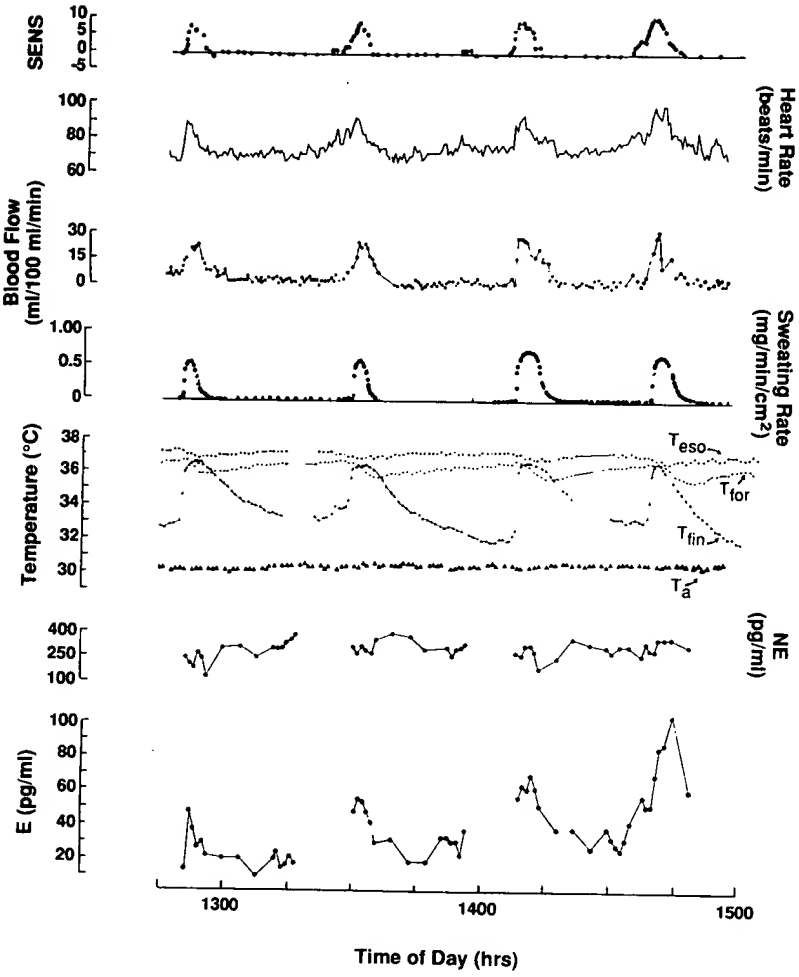

FIG. 7. Pattern of cardiovascular, thermoregulatory, and endocrine changes for four consecutive hot flashes over a 2-hr period. Changes in sensation (SENS), heart rate, blood flow (finger), sweating rate, temperatures (esophageal, forehead, finger, and ambient), norepinephrine (NE), and epinephrine (E) are depicted. (From ref. 85, with permission.)

TABLE 2. *Hormone changes during hot flashes*

Substance	Response	Reference
LH	Increase	35,38,39,46,68,69,120,121
FSH	No change	39,46,68,120
	Increase	38,69
GnRH	Increase	65
Estradiol	No change	46
Estrone	No change	46
Dehydroepiandrosterone	Increase	46
Androstenedione	Increase	46
Progesterone	Slight increase	46
Epinephrine	Increase	35,68
	No change	38,121
Norepinephrine	No change	38,68,120
	Decrease	35
	Increase	121
Dopamine	No change	38,121
Prolactin	No change	38,46,120
Cortisol	Increase	46,69,121
	No change	122
ACTH	Increase	46,69
β-Endorphin	Increase	46,69
β-Lipotropin	Increase	69
Neurotensin	Increase	123
Growth hormone	Increase	46
TSH	No change	46
Glucose	No change	121
Glucagon	No change	121
Insulin	No change	121

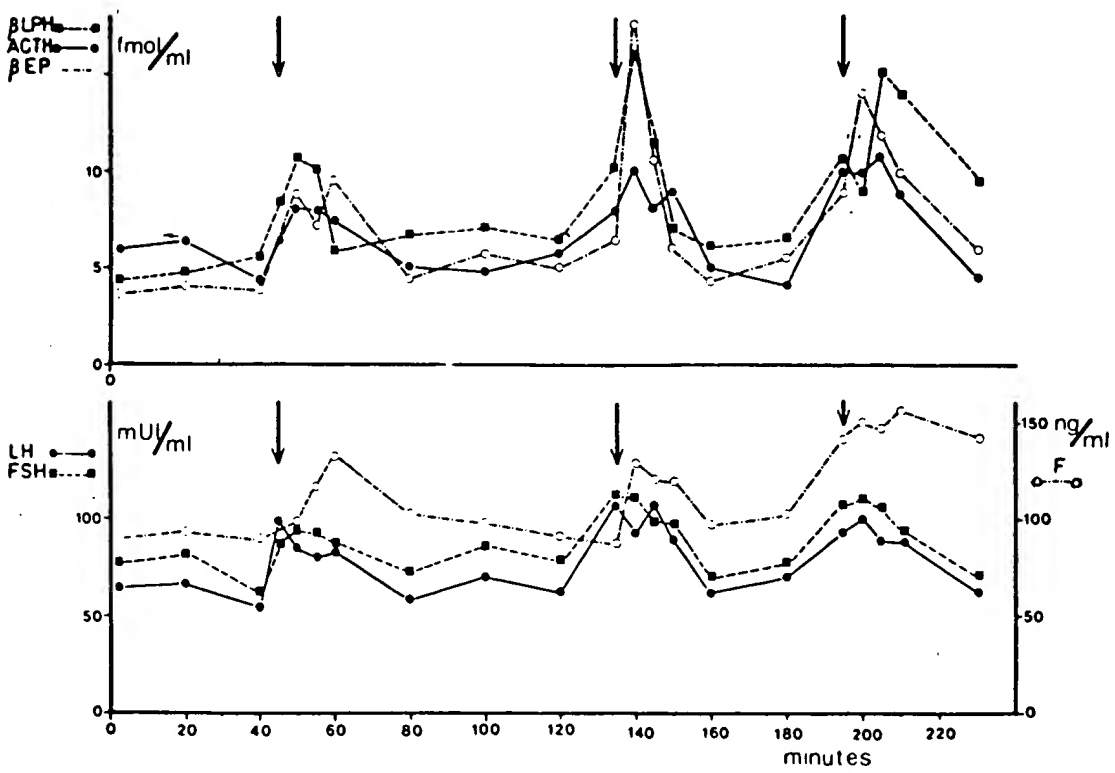

FIG. 8. Plasma levels of adrenocorticotropin (ACTH), β-lipoprotein (β-LPH), β-endorphin (β-EP) (**top**) and luteinizing hormone (LH), follicle-stimulating hormone (FSH), and cortisol (F) (**bottom**) in subject M.M. during observation period. *Arrows* indicate onset of hot flashes. (From ref. 69, with permission.)

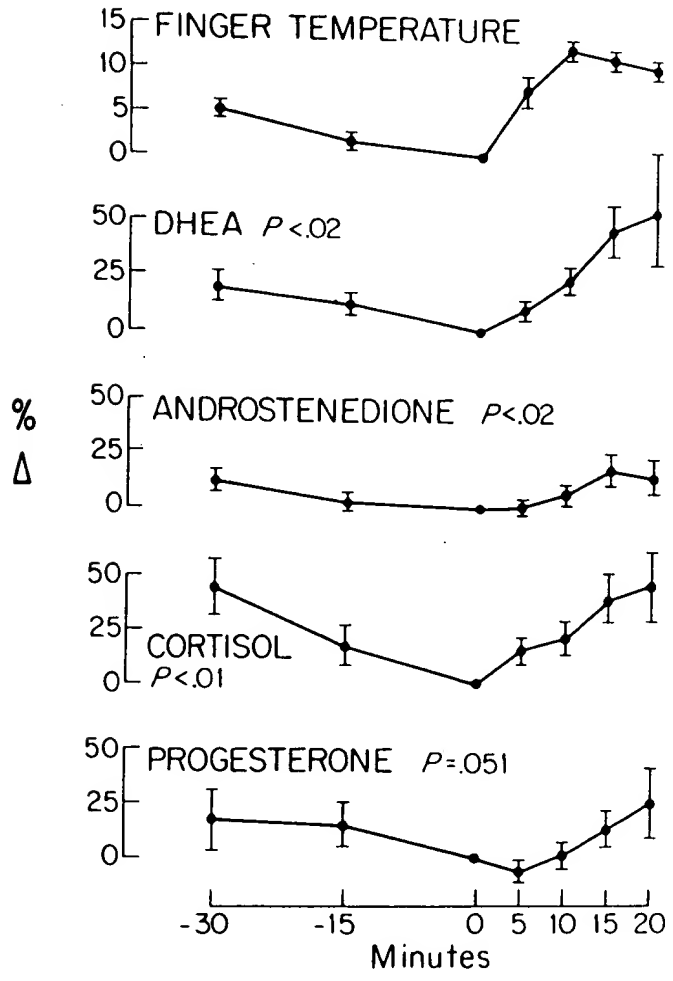

FIG. 9. Mean percent change of finger temperature and serum DHEA, Δ, F, and P levels before and after objective flashes. (From ref. 46, with permission.)

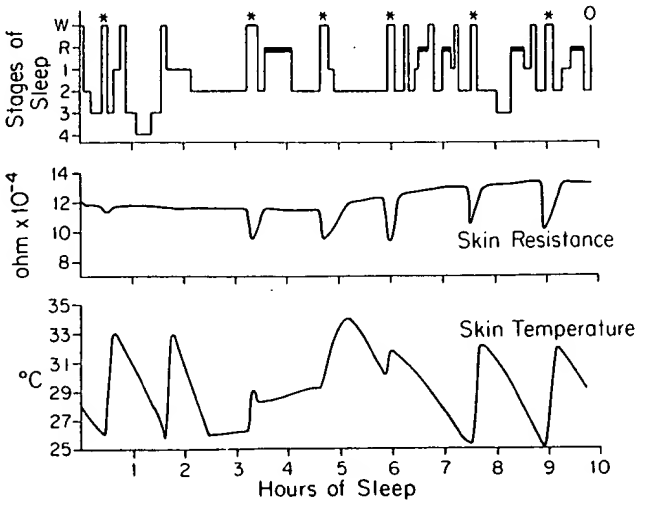

FIG. 10. Sleepgram and recordings of skin resistance and temperature in postmenopausal subject with severe hot flushes. Each *asterisk* marks occurrence of objectively measured hot flush. *Open circle* indicates arousal of patient by investigator at end of the study. (From ref. 71, with permission.)

of hot flashes are reduced with estrogen treatment (Fig. 11) (71,73,74). Sometimes, a woman may not consciously awaken from sleep (even though the EEG recording indicates momentary arousal), yet objective physiological measurement has documented the continuation of hot flashes throughout the night (Fig. 12). This sleep disturbance due to hot flashes is a primary motivator for women to seek medical advice and pharmacologic solutions. As is indicated later, a nonpharmacologic approach may also provide nighttime relief for some women.

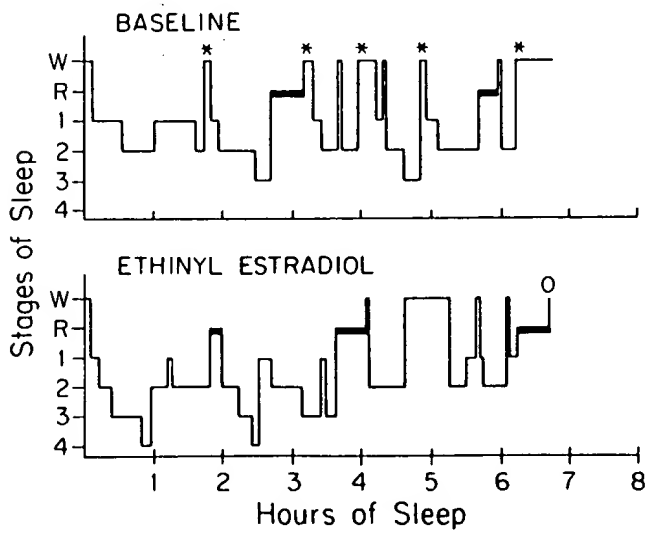

FIG. 11. Sleepgrams measured in symptomatic patient before and after 30 days' administration of ethinyl estradiol, 50 μg four times daily. (From ref. 71, with permission.)

AMBIENT TEMPERATURE AND HOT FLASHES

Many women find that their hot flashes are worse in warm weather. To relieve the discomfort of hot flashes, women may stand in front of an air conditioner or refrigerator, wear loose, light, nonsynthetic clothing, or, on cool nights, open windows. Yet scant research exists on the effect of ambient temperature on hot flashes. Hot flash frequency has been found by some investigators to correlate positively with outdoor temperature (75,76), while others found no relationship to exist (29,30). However, what has long been reported anecdotally, and in some uncontrolled thermal environments, has now been demonstrated under controlled temperature conditions. That is, ambient temperature does significantly influence both the frequency and intensity of hot flashes. In a cool environment (19°C) women had significantly fewer and less intense hot flashes than in a warm (31°C) environment (77) (Fig. 13). Cooling room temperature may therefore be one way in which women can reduce their hot flashes, particularly during sleep.

ETIOLOGY

Several hypotheses to explain the mechanism underlying hot flashes have been put forth (66,78–81). These hypotheses are based on data obtained primarily from studies of women with hot flashes in which substances measured in the peripheral circulation have been found to change in association with the hot flashes, or from observations on the success of various drugs in treating hot flashes. The hypotheses discussed most widely involve α-adrenergic mechanisms, endogenous opioid peptide, and GnRH. There have been a number of detailed reviews and critiques of the proposed models and theories to explain hot flashes (78,79,82–84). The definitive explanation still eludes us.

The hormonal milieu is obviously relevant to the occurrence of hot flashes. However, measuring the endocrine concomitants of hot flashes either in terms of mean hormone levels or episodic changes has not uncovered the initiating factor responsible for triggering a hot flash.

The sequence of events that characterizes a hot flash appears to be the result of a perturbation of the brain's thermoregulatory center located in the hypothalamus, activating mechanisms of heat loss (vasodilation, sweating, and behavioral adjustments) at hot flash onset, and heat conservation (vasoconstriction, behavioral changes, and shivering) at the termination. The combination and sequence of physiological and behavioral responses during a hot flash suggest that the phenomenon involves the coordinated action of the thermoregulatory system. The body responds as it

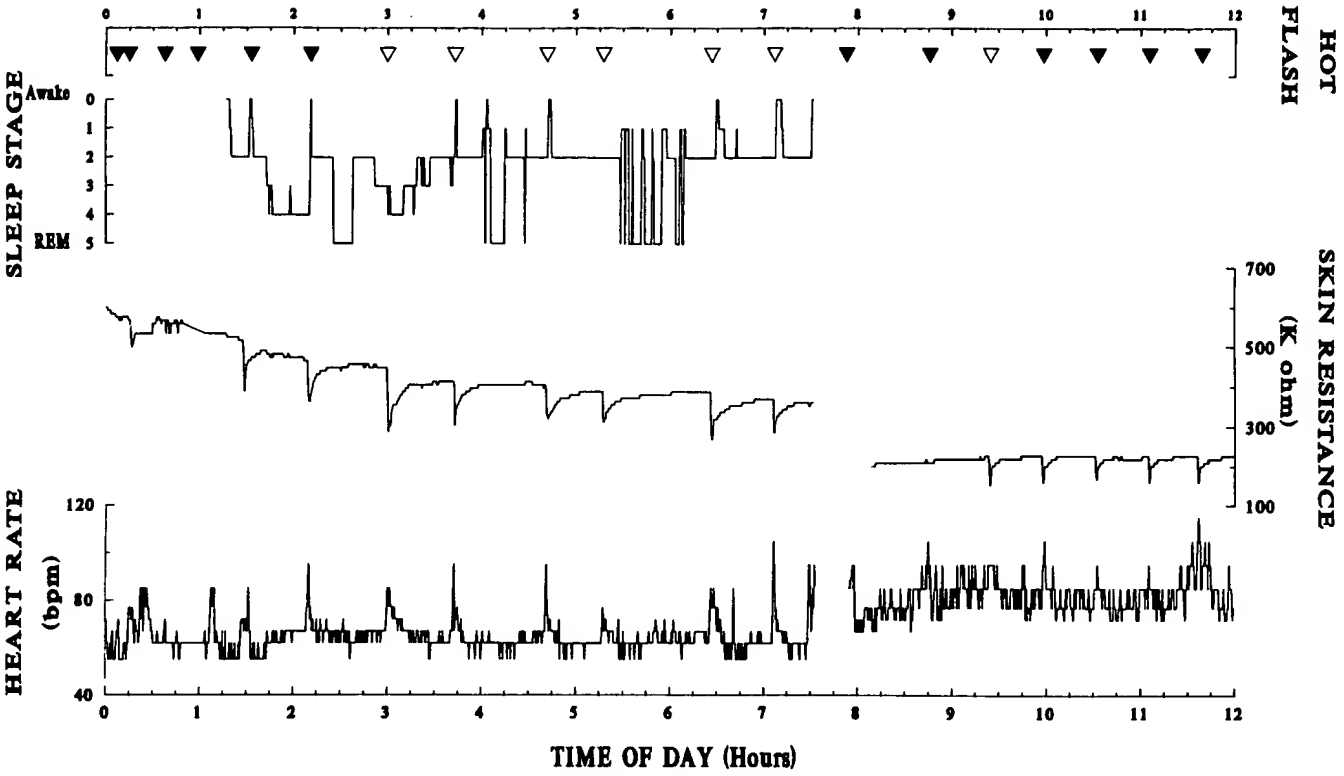

FIG. 12. Pattern of sleep stages, skin resistance, and heart rate for a 12-hr period (subject #A-10). The *solid triangles* (▼) indicate reported hot flashes; *open triangles* (▽) indicate unreported hot flashes. Sleep stages 1 through 4, NREM sleep; stage 5, REM (rapid eye movement); absolute clock time on the *abscissa*. The sudden drop in skin resistance at about 7:00 a.m. is due to a change of skin resistance electrodes. This subject went to bed shortly after 1:00 a.m. and awoke at about 7:30 a.m. (From ref. 14, with permission.)

would to dissipate excess heat in situations of overheating or at the breaking of a fever. Since there is no elevation of internal temperature associated with a hot flash, however, the responses are consistent with the hypothesis that a hot flash involves a transient downward resetting of the body's thermoregulatory set-point (36,85). In other words, at the start of a hot flash there is a sudden drop in set-point temperature. Since the body would then be warmer than this new set-point, the thermoregulatory system acts appropriately to cool the body. As a result, internal temperature falls. The set-point then returns to normal, and heat conservation mechanisms act to return body temperature to normal. This entire process is analogous to what happens during a fever, but the change in set-point is in the opposite direction than during fever (36,85). Pyrogenic substances can raise the set-point temperature and initiate the thermoregulatory responses that result in a fever (86). What remains unknown is precisely what causes the hypothalamic resetting during a hot flash.

Possible candidates include endocrine and neuroendocrinological substances. Reproductive hormones modulate the functioning of the thermoregulatory sys-

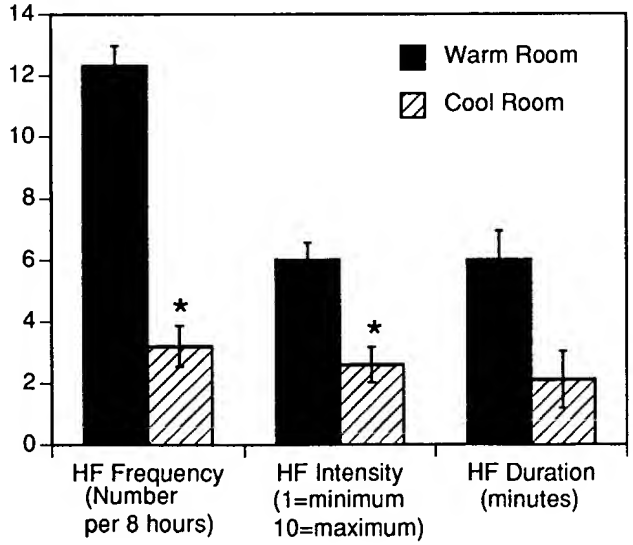

FIG. 13. Mean frequency, intensity, and duration of hot flashes at warm (31°C) versus cool (19°C) ambient temperatures ± 1 SEM. $^*p < 0.05$. The units of the *y*-axis vary with parameter, as indicated. (From ref. 77, with permission.)

tem (85), as do opioid peptides (87–89), which also modulate and are influenced by reproductive hormones (90–92). Further delineation of the relationship between sex steroids, opioid peptides, and thermoregulatory function is necessary.

A coherent hypothesis should be able to accommodate the hot flash-associated thermoregulatory and neuroendocrine responses, and be able to explain among other things: (a) why different individuals experience hot flashes at different frequencies and for varying lengths of time, and why some women never get hot flashes; (b) why hot flashes begin in some women just hours after ovariectomy; (c) why some women sweat while others do not; (d) why priming with estrogen is necessary before hot flashes can occur (no hot flashes are seen in prepubertal girls, or women with gonadal dysgenesis before treatment with estrogen); (e) the similar phenomenon of hot flashes in women and men following a reduction in estrogen in women or testosterone in men; (f) the observations that drugs such as clonidine have been demonstrated to eliminate the sensation of hot flashes, while pulses of finger temperature and LH remain. Are there invariant components of a hot flash that are always measurable, independent of environmental conditions, age, or sex? A resolution of these questions awaits additional research, and perhaps an animal model that more closely resembles the human female in terms of both endocrine and thermoregulatory functioning.

WHY ARE HOT FLASHES A PROBLEM?

If hot flashes occur only sporadically, they are not likely to be disruptive or even much greater than a nuisance. But for those women with many hot flashes throughout the day, every day, hot flashes can be periodically disabling, physically draining, and can impact negatively on work, family, and social relationships. When hot flashes disturb sleep every night, the consequences can be debilitating. Some women choose to avoid touching, hugging, or sexual activity because the skin-to-skin contact may bring on a hot flash.

Profuse sweating during a hot flash is one of the most bothersome complaints; it can be an embarrassment, particularly at work or in social situations. It may even require a change of clothing, which is not always possible or convenient. Women with severe hot flashes describe their lives as a constant struggle to achieve thermal comfort. They must adjust their behavior (such as wearing layers of clothes for easy removal, shunning synthetics for natural fibers, or carrying a fan), or they attempt to alter their immediate environment by turning on the air conditioner, opening windows, going outside if the weather is cool, or staying inside on hot humid days.

DIAGNOSIS

Most women who present with hot flashes will be perimenopausal or recently postmenopausal. Therefore age and menstrual history (menstrual cycle irregularity, oligomenorrhea or amenorrhea) give strong indications that these are menopausally related hot flashes, as do other complaints suggestive of low estrogen, such as vaginal dryness and its sequelae. During the perimenopausal period, hot flashes may come and go. Menstrual cycle irregularity may correspond with these fluctuating episodes. If women are still menstruating regularly when hot flashes first occur, they may not recognize that the episodes of feeling hot and sweating are actually hot flashes. Thus there may be many years of hot flashes prior to menopause. And hot flashes may continue long into the postmenopausal years, and sometimes throughout a woman's lifetime.

In the few cases where diagnosis of hot flashes is unclear, it may be of value to measure plasma follicle-stimulating hormone (FSH) and LH, since they are both elevated in menopausal women. However, particularly during the perimenopause, levels of these hormones fluctuate. So multiple measurements would have to be made. FSH is better diagnostically than LH since the increase in circulating LH tends to lag behind the rise in FSH. Estradiol is not a particularly good indicator on which to base diagnosis in women of pre- and perimenopausal ages.

Several conditions share some clinical features with hot flashes, particularly the flushing and sweating. These include hyperthyroidism, panic attacks, carcinoid syndrome, pheochromocytoma, and niacin flush.

MANAGEMENT

Many women can make adjustments necessary to cope with their hot flashes if they are provided with adequate information and support. Women can experience a wide range of sensations during hot flashes. This may be upsetting if they are unaware of what to expect. Many of the worries of women with hot flashes can be allayed if they are informed of what is and what is not known. They could be told, for example, that no one can predict exactly how long their hot flashes will last or, therefore, the necessary duration of treatment. It is also important to convey that hot flashes may recur when treatment is ended.

The initial stages of management should include a determination of the level of impact of the hot flashes and an assessment of how the woman has been coping with them. Precipitating factors such as hot drinks, alcohol, caffeine, or hot environments should be identified and avoided. Stresses at home or in the workplace may also make hot flashes even more difficult to cope with.

Many women try to control their hot flashes by modifying their environment or behavior before consulting a physician. They change room temperature, wear light, layered clothing, and try vitamins or dietary changes that have been suggested to them. For some, these attempts may be effective and the hot flashes may become less intense or less frequent. While for others, nothing they do has any impact on their relentless hot flashes. When knowledge, proscription, and behavioral changes prove insufficient, women may ask about hormone therapy.

Pharmacologic Preparations

The available therapies do not "cure" hot flashes; rather, they provide symptomatic relief by making the hot flashes less frequent and/or less intense, or sometimes by eliminating them, at least for the duration of the treatment. If hot flashes return when treatment is stopped, it is not known whether the treatment just postponed the hot flashes, or whether the individual would have had hot flashes for that duration regardless of whether she had been treated. To minimize the recurrence of hot flashes, it is advisable to taper drug treatment over several weeks, rather than stopping suddenly. We do not know the mechanism by which hot flashes are reduced for any of the treatments discussed below.

When various hot flash therapies are compared with a placebo, the placebo often demonstrates considerable effectiveness. Therefore to best assess the efficacy of a treatment, it is necessary to conduct randomized, double-blind, placebo-controlled crossover studies. And, as it may take several weeks to effectively control hot flashes, studies must be of sufficient duration to adequately determine how well a particular treatment works.

Estrogen

Estrogen administration is currently the most effective treatment for hot flashes. It has been used, albeit initially in the form of crude extracts, for almost 100 years. The rationale is based on the association of hot flashes with the decline in ovarian function at menopause rather than on the knowledge of the cause of hot flashes.

The effect of estrogen treatment on hot flashes is not usually immediate. The full benefit may not be realized until several months of therapy. When treatment is discontinued, the effect on hot flashes may persist for some time, depending on the type of estrogen or route of administration. For example, conjugated equine estrogen may remain active for several weeks after treatment has ended, due to storage in adipose tissue (93). Many patients on a cyclic estrogen regimen may find that, for each cycle, it takes several days before hot flashes diminish, and by the end of the week in which no estrogen is taken, hot flashes have returned. For this and other reasons, the current trend is toward prescribing continuous daily estrogen.

The most commonly used regimen for treating hot flashes in the United States is 0.625 to 1.25 mg of oral conjugated equine estrogen (Premarin). Many other oral preparations are available in equivalent doses (see Chapter 6). Transdermal estradiol (Estraderm 0.05 to 0.10 mg/day) has been gaining popularity. Estrogen is also available as subcutaneous implants, injectables, and vaginal creams. Most are effective in treating hot flashes.

Oral estrogen has been in use for many years and has been the most extensively studied of the treatments for hot flashes. In a double-blind, placebo-controlled crossover study of conjugated equine estrogen (1.25 mg), Coope et al. (94) reported that after the first 3 months, hot flashes were reduced by about 90% in women on estrogen and by about 62% in women on placebo (Fig. 14). In another placebo-controlled trial, Campbell and Whitehead (95) sought to assess the efficacy of conjugated estrogen (1.25 mg) in relieving hot

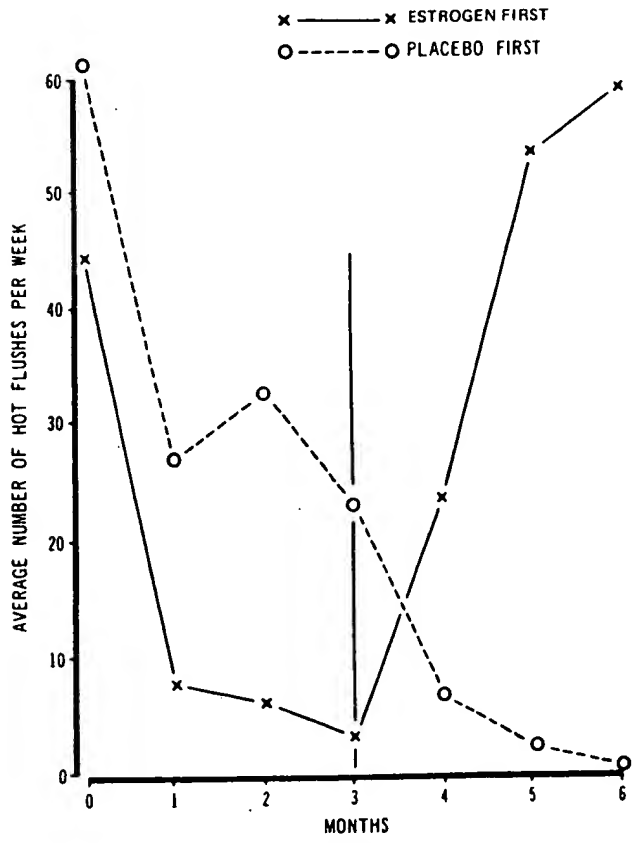

FIG. 14. Hot flush count during the 6-month trial. (From ref. 94, with permission.)

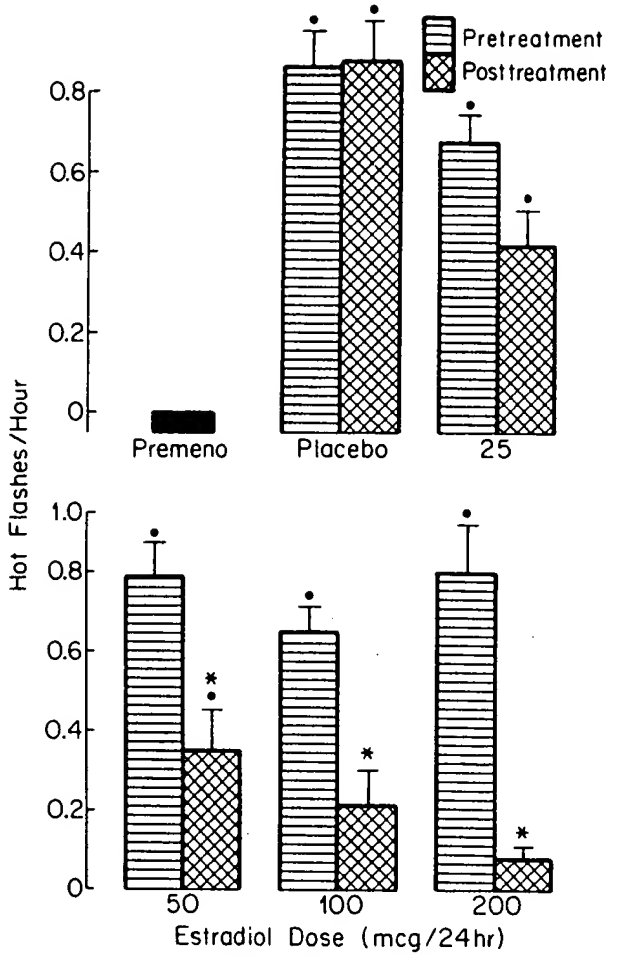

FIG. 15. Mean ± SE rate of occurrence of hot flashes in the study groups and premenopausal women (Premeno) before and during transdermal E_2 administration. (From ref. 96, with permission.)

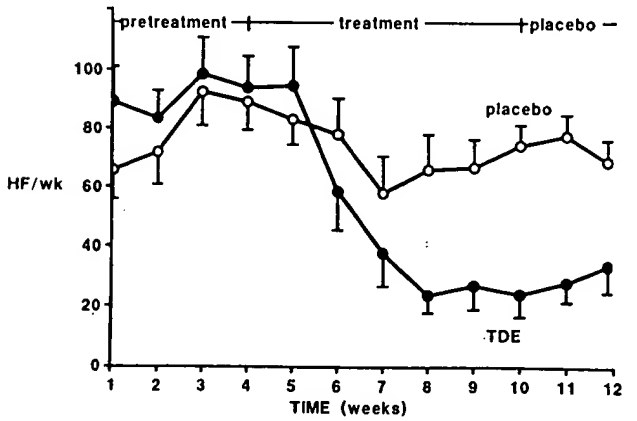

FIG. 16. Total subjective hot flashes (HF) recorded by patients on transdermal estradiol (TDE) patch (N = 10) and placebo (N = 8, first seven weeks; N = 7, last five weeks) for each study week. (From ref. 97, with permission.)

flashes and other symptoms of menopause such as vaginal dryness, insomnia, anxiety, irritability, and memory loss. Estrogen was significantly better than placebo in improving all these symptoms. Hot flashes were improved by 40% to 50% with estrogen and by approximately 10% with placebo (as assessed by graphic rating scores). In this study, one group of subjects had symptoms such as insomnia, but they did not have hot flashes. Treatment with estrogen improved some of their symptoms, but not their insomnia. This is in contrast to the alleviation of the insomnia for those women who also complained of hot flashes. The investigators concluded that much of the insomnia of women with hot flashes is the result of nocturnal hot flashes.

Transdermal patches provide a continuous diffusion of estradiol and are effective in reducing hot flashes. A dose–response relationship between dose of transdermal estradiol (25, 50, 100, and 200 μg/24 hr) and hot flash frequency, using subjective and objective criteria, was demonstrated in a double-blind study by Steingold (96) (Fig. 15). Hot flashes were significantly reduced at all doses of estradiol, with a progressive decline in hot flashes as estradiol increased; hot flashes were not appreciably reduced by placebo. The highest dose of 200 μg/day resulted in a 91% reduction in the number of hot flashes.

Haas et al. (97) compared the effects of 6 weeks of transdermal estradiol (10 cm^2, 50 μg/day) with that of placebo, on subjectively and objectively measured hot flashes in a double-blind, placebo-controlled study. While changes in plasma estradiol and LH levels were measurable within 8 hr of the application of the patch, a decline in hot flashes occurred only gradually over the next 4 weeks. At that point there was a 74% decrease in subjectively reported hot flashes and an 85% decrease in objectively monitored hot flashes (Fig. 16). Women on placebo reported a 27% reduction in hot flashes (not statistically significant) during the first 3 weeks of the study.

Stanczyk (98) compared transdermal estradiol with subdermal estradiol. Hot flashes were eliminated in all patients, regardless of the mode of estrogen delivery.

In addition to ameliorating hot flashes, other complaints that may be improved by estrogen include insomnia (74,95), vaginal dryness (95), memory/concentration (95), lower urinary tract problems (95), and mood (95,99).

Nonestrogenic Treatments

Although most women find that estrogen relieves their hot flashes, there are some for whom estrogen is contraindicated or who find the side effects unacceptable, some whose hot flashes are not responsive to es-

trogen, even at elevated doses, and others who prefer not to remain on estrogen for a prolonged period of time.

Progestins

Medroxyprogesterone acetate (MPA) is a nonestrogenic steroid. Several double-blind, placebo-controlled studies have shown that MPA decreases the number of hot flashes. Injected intramuscularly, a dose of 150 mg/month MPA resulted in a 90% reduction in hot flashes, compared with a 25% reduction in the placebo group (100). The major side effect was abnormal uterine bleeding (43%). Morrison et al. (101) conducted a study of MPA (50, 100, and 150 mg im) in which a dose–response relationship was shown, with about 75% improvement for those on 50 mg, and 90% to 100% relief for those on 150 mg by week four of treatment. Most women in the placebo group dropped out of the study. For those who remained, the placebo was ineffective. In this study, only two subjects on MPA (of 36 women) had abnormal bleeding.

Taken orally, MPA has fewer side effects. In a double-blind, placebo-controlled trial, MPA (20 mg/day) resulted in an approximately 74% decline in the number of reported hot flashes by the third month of treatment; placebo caused a reduction in hot flashes of about 26% (Fig. 17) (102). Albrecht et al. (103) measured hot flashes both subjectively and objectively in response to 20 mg/day, oral MPA. Reported hot flashes decreased by 90% in women on MPA and by 25% in those on placebo. Finger skin temperature elevations and associated LH pulses, the objective indicators of hot flashes, were also reduced.

Another progestin, megestrol acetate (MA), has been tested and found to be effective in treating hot flashes. Oral MA significantly reduced hot flashes (no placebo control) whether measured subjectively or objectively, in a dose–response fashion with increasing doses of MA (20, 40, 80 mg/day) (Fig. 18). Few side effects were reported, and no abnormal bleeding or depression (124).

Sherwin and Gelfand (104) compared women on conjugated equine estradiol alone, with those on estradiol + medroxyprogesterone acetate (MPA). Both regimens resulted in a reduction in hot flashes. Estradiol was administered on days 1 to 25, and MPA on days 15 to 25, leaving days 26 to 30 hormone-free. For 3 weeks of each cycle hot flashes were diminished. During the fourth week, which was hormone-free, hot flash frequency increased.

Clonidine

Clonidine, an α-adrenergic receptor agonist that influences vascular responsiveness, has been used in the treatment of hot flashes. Clayden and colleagues (105) reported a double-blind, placebo-controlled crossover study of 86 women with hot flashes, and they demonstrated that clonidine (0.05 to 0.15 mg/day) reduced the

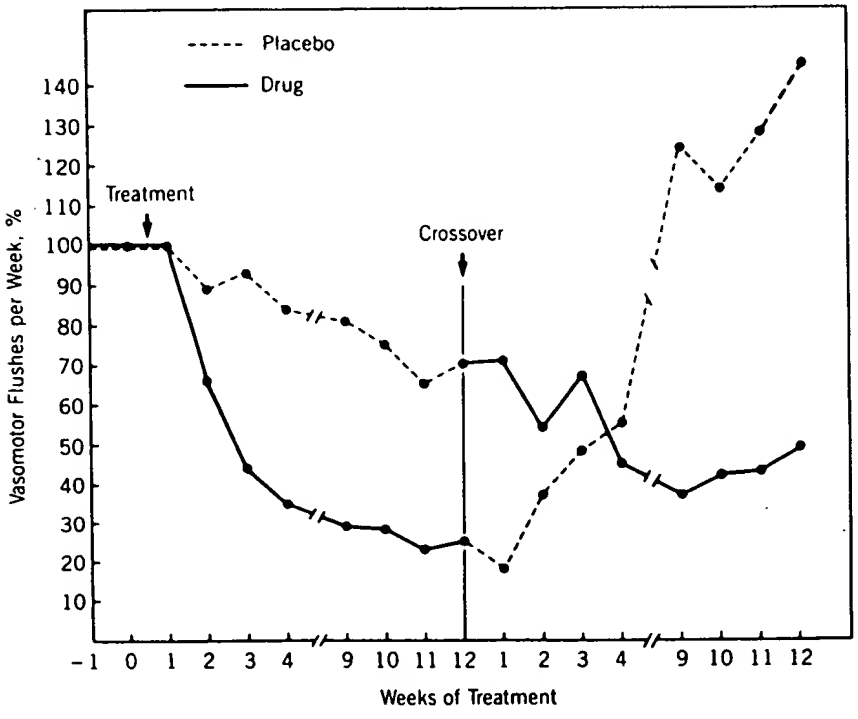

FIG. 17. Effect of oral medroxyprogesterone acetate on frequency of hot flashes. Mean number of vasomotor flushes as a percent change from pretreatment (week −1 to 0). (From ref. 102, with permission.)

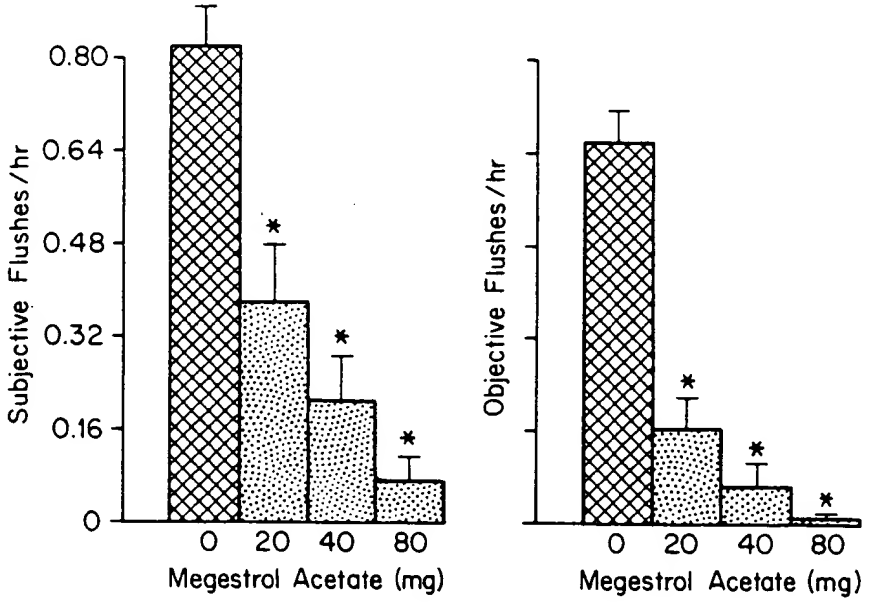

FIG. 18. The mean (±SE) subjective and objective flushes per hour before and following the oral administration of the various doses of megestrol acetate. *Significantly different ($p < 0.01$) from baseline. (From ref. 124, with permission.)

number and intensity of hot flashes. However, as in the studies of estrogen, women on placebo also reported a reduction in hot flashes almost equal to that of women on clonidine (Fig. 19). Dry mouth was the primary complaint of those on clonidine. Other side effects, including insomnia, headache, depression, and nausea, were reported both by those on clonidine and on placebo. In another study, Laufer and co-workers (106) demonstrated a dose–response relationship between clonidine (0.1, 0.2, 0.4 mg/day) and objectively recorded hot flashes in six women. At the highest dose, reduction in hot flashes was 46%; the reduction with placebo was small and not statistically significant. Of the initial 10 subjects, four withdrew due to side effects, which included nausea, fatigue, headaches, dizziness, and dry mouth.

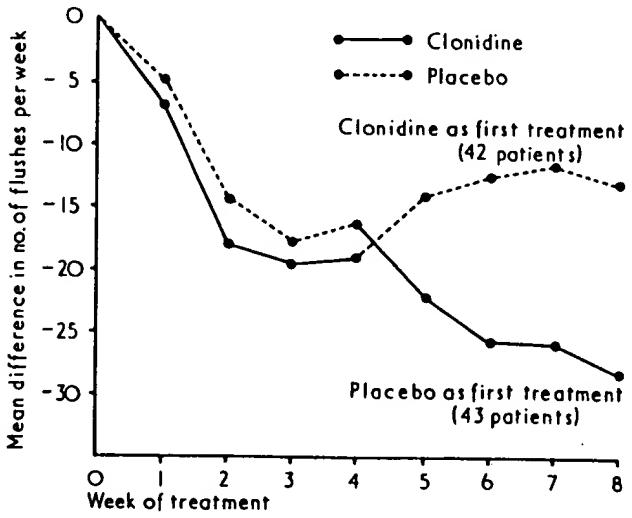

FIG. 19. Mean change in number of flushes from initial values. (From ref. 105, with permission.)

When clonidine was administered intravenously to menopausal women with hot flashes, Tulandi et al. (107) obtained somewhat different results. Subjects who received clonidine (0.075 mg in 10 ml physiological saline) did report significantly fewer hot flashes; however, objective recordings indicated a continuation of the pattern of episodic increases in finger skin temperature and the associated pulses of LH characteristic of hot flashes.

Ginsburg et al. (108) examined vascular responsiveness in menopausal women before and after oral clonidine treatment. They measured peripheral vasodilatory responses to infusion of the vasoactive substances norepinephrine, epinephrine, and angiotensin. Forearm and hand blood flow responses in the infusions were diminished after clonidine treatment. The investigators suggest that clonidine might reduce the peripheral vasodilation that accompanies a hot flash, and that given the reduced response to angiotensin, clonidine might be acting in some way other than through peripheral adrenergic mechanisms.

Lofexidine, another alpha-agonist, and α-methyldopa, whose primary metabolite, α-methylnorepinephrine, is an α-receptor agonist, have also demonstrated effectiveness in reducing hot flashes (109,110).

Propranolol

Propranolol, a peripherally and centrally acting beta-receptor blocking agent, has been studied with

mixed results. Erkkola and colleagues (111) reported that 60 mg/day of propranolol slightly reduced hot flashes. The reduction was from approximately 9.4 hot flashes/day to 7.8 hot flashes/day. There was no placebo control. Coope et al. (75), in a randomized double-blind placebo-controlled trial, found 40 mg of propranolol daily to be no more effective than placebo in reducing hot flashes. The slight reduction in hot flashes was similar to that reported by Erkkola. No side effects were seen among the women on propranolol. A statistically significant reduction in hot flash frequency was reported by Alcoff et al. (112) in 70% of their subjects. However, there was no report of the extent of the reduction, so it is difficult to assess whether this had clinical significance. Side effects (including lightheadedness, nausea, and fatigue) occurred in 24% of those on propranolol (80 mg/day).

Bellergal

Bellergal is a combination of belladonna alkaloids, ergotamine tartrate, and phenobarbital. In a double-blind, placebo-controlled study, Lebherz and French (113) found Bellergal to be significantly more effective than placebo are reducing subjectively reported hot flashes (60% decrease in hot flashes versus 22% decrease, respectively). The specific mechanism of action on hot flashes is unknown. Bellergal has sedative effects and is not a treatment of choice. One must also consider the varied actions of the three components and be aware of possible interactions with other drugs.

NONPHARMACOLOGIC APPROACHES

The impetus to explore alternative therapies springs not from a pressing need for a more effective treatment, since estrogen is very effective, but primarily from a concern over the safety of estrogen treatment, and a need for alternatives for those for whom estrogen is contraindicated, who cannot tolerate estrogen, or who choose not to take estrogen. Unfortunately, the therapeutic efficacy of most alternatives has not been adequately tested.

Ambient Temperature

As indicated earlier, the surrounding air temperature can have a significant impact on both the frequency and intensity of hot flashes. For women who have difficulty sleeping due to frequent hot flashes, maintaining a cool bedroom temperature is one way to ameliorate hot flashes and reduce nighttime awakenings. It is not as easy to control the temperature of one's environment during the day, but if possible to achieve, a cool environment would reduce hot flashes.

Vitamin E

In the 1940s a number of studies tested the effectiveness of vitamin E in treating hot flashes (114–116). Most of these investigations found vitamin E to have value in treating hot flashes. But the studies were neither double-blind nor placebo-controlled. In 1953, Blatt et al. (117) conducted a double-blind study comparing the effect of vitamin E, estrogen, and a placebo (no crossover) on a complex of menopausal symptoms (not hot flashes alone, but as part of a group of 11 symptoms). They found vitamin E to be no more effective than placebo, and considerably less effective than estrogen in treating this symptom complex. This study is often quoted as demonstrating the lack of effectiveness of vitamin E for treating hot flashes, a conclusion that cannot be drawn from the data. Some women report anecdotally that vitamin E is very effective in ameliorating their hot flashes (F. Kronenberg, *unpublished data*). A properly controlled study of vitamin E and hot flashes is warranted in order to determine the degree of effectiveness and for whom the treatment might be most effective.

BEHAVIORAL TREATMENTS

Behavioral methods for moderating hot flashes have received limited study. Freedman and Woodward (81) compared paced respiration and muscle relaxation for their effects on objectively recorded hot flashes. Paced respiration training significantly reduced the frequency of hot flashes (by about 40%) as compared with progressive muscle relaxation training. A variety of behavioral modalities should be evaluated in rigorously designed studies.

Acupuncture

Studies to evaluate the effectiveness of acupuncture in treating hot flashes are underway. Preliminary data from Hammar and colleagues (118) suggest that electrostimulated acupuncture decreases the frequency of hot flashes. Data are as yet insufficient to make possible conclusions or recommendations.

Exercise

The effect of exercise on hot flashes is being investigated. Hammar et al. (119) found that women who belonged to a "gymnastic club" reported less severe

hot flashes than women who did not belong. They did not, however, investigate the physical activity of the latter group. Since exercise results in a great variety of physiological changes, a more rigorous study is needed to determine what component of exercise-induced responses might be responsible for the amelioration of hot flashes.

Diet

Information on how specific foods affect hot flashes is anecdotal. Some women report that caffeine, alcohol, or spicy foods seem to trigger hot flashes. Eliminating foods suspected of aggravating hot flashes can be tried. No scientific data are available regarding either short-term trigger effects or longer-term effects of dietary patterns on hot flashes.

CONCLUSION

We have gained considerable knowledge about hot flashes over the past two decades, although many questions remain unanswered and the specific genesis of hot flashes remains unknown. Even the role of estrogen in the etiology of hot flashes, or the mechanism by which estrogen relieves hot flashes, is still not understood.

While the patterns of hot flashes may be varied, there are commonalities in their physiology and subjective manifestations. Yet the significance of hot flashes to an individual woman's quality of life varies greatly. Currently in the United States there are about 40 million women of menopausal age. The majority of women will at some time experience hot flashes, and for most of these women, hot flashes will last 1 to 3 years and will not be particularly frequent or disruptive. However, 3 to 5 million women will have severe and frequent hot flashes that can be physically and psychologically debilitating. These are the women who most likely would seek medical assistance.

During a hot flash, elements of thermoregulatory, cardiovascular, and endocrine systems act in concert. These elements simultaneously serve other, nonthermal functions such as keeping blood flow and blood pressure regulated. It is an immense challenge to the researcher, given physiological complexity, to produce an explanation of hot flashes that integrates these various interacting physiological factors, as well as behavioral, psychophysiological, and even psychosocial components. Understanding the cause of hot flashes would provide insights into normal and abnormal changes at menopause. A more complete knowledge of the thermoregulatory, cardiovascular, and psychophysiology of women with hot flashes as compared to women without hot flashes may enable us to predict who is most likely to be affected, and to identify additional approaches to the management and treatment of hot flashes.

As information increases about factors that are predictive of hot flashes, and about other heath problems that can influence treatment choice, an individualized approach is increasingly indicated. One dose, regimen, or approach does not fit all women. This makes it all the more urgent to understand the underlying physiology, so we can broaden the treatment options available to women.

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THE HENRY J. KAISER FAMILY FOUNDATION

Prescription Drug Trends

a chartbook

july 2000

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July 2000

Top 20 Prescription Drugs Ranked by Number of Dispensed Prescriptions, 1998

exhibit 3.16

Rank	Product	Indication	1998 Prescriptions Dispensed (Million)	Brand or Generic?	Year First Marketed
1	Premarin (Wyeth-Ayerst)	hormone replacement	46.8	B/G	1964
2	Synthroid (Knoll)	thyroid replacement	38.8	B/G	1963
3	Hydrocodone w/APAP (Watson)	narcotic analgesic	29.4	G	1977
4	Trimox (Apothecon)	antibiotic	28.5	G	1977
5	Prilosec (Astra-Merck)	anti-ulcerant (proton pump inhibitor – PPI)	26.7	B	1989
6	Albuterol (Warrick)	bronchodilator	26.0	G	1982
7	Lipitor (Parke-Davis/Warner Lambert)	cholesterol-lowering	24.9	B	1997
8	Prozac (Dista/Lilly)	SSRI anti-depressant	24.8	B	1987
9	Lanoxin (Allen & Hansbury)	cardiotonic (for heart failure)	24.2	B/G	1967
10	Norvasc (Pfizer)	calcium channel blocker (for hypertension)	23.4	B	1992
11	Claritin (Schering)	antihistamine	22.3	B	1993
12	Zoloft (Roerig/Pfizer)	SSRI anti-depressant	21.0	B	1992
13	Paxil (SmithKline Beecham)	SSRI anti-depressant	19.0	B	1993
14	Vasotec (Merck)	calcium channel blocker (for hypertension)	18.5	B	1986
15	Zocor (Merck)	cholesterol-lowering	18.5	B	1992
16	Prempro (Wyeth-Ayerst)	hormone replacement	18.3	B	1995
17	Coumadin Sodium (DuPont)	anti-coagulant	17.9	B/G	1954
18	Zestril (Zeneca)	ACE inhibitor (for hypertension)	17.5	B	1988
19	Glucophage (Bristol-Myers Squibb)	anti-diabetic agent	17.2	B	1995
20	Augmentin (SmithKline Beecham)	antibiotic	15.7	B/G	1984

notes

B = Brand name (has remaining patent life; no generic versions available).

B/G = Brand name product but generics available.

G = Generic.

Rankings and number of prescriptions represent total prescriptions dispensed through independent, chain, foodstore, long-term care, and mail order pharmacies.

sources

Sonderegger Research Center analysis, based on:

Prescriptions Dispensed from IMS Health, Inc., *National Prescription Audit (NPA) Plus*, published in *Medical Marketing & Media*, May 1999.

Year First Marketed from Top 200 listing published in *Pharmacy Times*, April 1999.